CHAPTER 1

THE McMURRY COUPLING AND RELATED REACTIONS

TAKESHI TAKEDA AND AKIRA TSUBOUCHI

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

CONTENTS

	PAGE
INTRODUCTION	3
MECHANISM	5
STEREOCHEMISTRY	8
SCOPE AND LIMITATIONS	11
Coupling Reagents	11
Low-Valent Titanium-Based Reagents	11
The $TiCl_4$–Zn System	11
The $TiCl_3$–Zn/Cu System	12
The $TiCl_3$–$LiAlH_4$ System	12
The $TiCl_3$–Alkali or Alkaline Earth Metal System	12
The $TiCl_3$–Lithium Arene System	13
The $TiCl_4$–BuLi System	13
Supported Titanium Reagents	13
Titanium Powder	13
Other Titanium-Based Reagents	14
Low-Valent Metals Other Than Titanium	14
Aluminum and Zinc Reagents	14
Zirconium Reagents	14
Vanadium and Niobium Reagents	15
Molybdenum and Tungsten Reagents	15
Indium Reagents	15
Samarium and Ytterbium Reagents	15
Uranium and Thorium Reagents	16
Effect of Additives	16
The Carbonyl Substrate	17
Aldehydes	18
Ketones	19
Esters	19
Amides	20
Carboxylic Acids and Acid Halides	21
Related Substrates	21

takeda-t@cc.tuat.ac.jp

Organic Reactions, Vol. 82, Edited by Scott E. Denmark et al.

© 2013 Organic Reactions, Inc. Published 2013 by John Wiley & Sons, Inc.

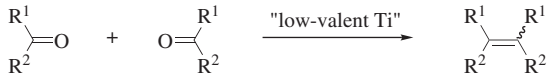
Mode of Coupling of Aldehydes and Ketones 22
Homocoupling 22
Mixed-Coupling 22
Intramolecular Coupling 24
Tandem Cyclizations (Annulations) 25
Related Reactions 26
Carbonyl Olefination with *gem*-Dihalides 26
Carbonyl Olefination with Thioacetals 28
APPLICATIONS TO SYNTHESIS 30
Synthesis of Sterically Hindered and/or Strained Alkenes 31
Synthesis of Highly Conjugated Molecules 32
Synthesis of Ring Compounds with Unique Structures 37
Synthesis of Cyclophanes, Helicenes, and Related Compounds 39
Total Synthesis of Natural Products 41
COMPARISON WITH OTHER METHODS 44
Wittig and Related Reactions 44
Peterson Olefination 45
Julia–Lythgoe and Julia–Kocienski Reactions 45
Carbonyl Olefination with Metal Carbene Complexes and Related Reactions . . 46
EXPERIMENTAL CONDITIONS 47
Preparation of Coupling Reagents: Stepwise vs One-pot Procedures . . . 47
General Comments for the Preferred Conditions 48
Coupling Reagent 48
Solvent 48
Temperature 50
High-Dilution Methods for Intramolecular Coupling 51
Catalytic McMurry Coupling 52
EXPERIMENTAL PROCEDURES 52
trans-1,2-bis(3-Methylthio-2-naphthyl)ethene [Homocoupling with the $TiCl_4$–Zn System] 52
(*E*)-8,9-bis(4-Bromophenyl)-8-hexadecene [Homocoupling with the $TiCl_4$–Zn–Py System] 53
5,16-Dihydrotetrathia[22]annulene[2,1,2,1] [Tandem Coupling with the $TiCl_4$–Zn–Py System] 54
(+)-Aristoteline [Intramolecular Coupling with the $TiCl_3$–Zn System by the "Instant Method"] 54
ansa-(Vinylene)ferrocene [Intramolecular Coupling with the $TiCl_3$–Zn/Cu System] 55
trans-1,2-bis(5-(Benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene [Homocoupling with the $TiCl_3(DME)_{1.5}$–Zn/Cu System] 55
1,2-Di-*tert*-butylcyclopentene [Intramolecular Coupling with the $TiCl_3(DME)_{1.5}$–Zn/Cu System] 56
1-Isopropylidene-3a-methyl-4a-(*tert*-butyldimethylsiloxy)-2,3,3a,4,4a,5,6,7-octahydrocyclobuta[1,2:1,4]dicyclopentene [Mixed-Coupling with the $TiCl_3$–Li System] 56
l5,16-Diphenyl-l,4,7,10-tetraoxa(10.2)[20]paracyclophan-15-ene [Intramolecular Coupling with the $TiCl_3$–Na/Al_2O_3System] 57
2-(3,5-Dimethoxyphenyl)-5,6-dimethoxy-3-methylindole [Intramolecular Coupling with the $TiCl_3$–C_8K System] 57
(±)-Acoragemacrone [Intramolecular Coupling of a Keto Ester with the $TiCl_3$–$LiAlH_4$ System] 58
3-Phenyl-2-trifluoromethylindole [Intramolecular Coupling with the Catalytic $TiCl_3$–Zn–TMSCl System] 58

9,9-Bisfluorenylidene [Homocoupling with the Commercial Titanium Powder–TMSCl System] . . . 59
1,2-Dipiperidinostilbene [Homocoupling with the Yb–YbI_2 System] . . . 59
2-Methoxy-1-(trimethylsilyl)tridec-1-ene [Carbonyl Olefination with the CH_2X_2–Zn–$TiCl_4$ System] . . . 60
2-Ethoxy-1-phenylnon-1-ene [Carbonyl Olefination with the RCH $(SPh)_2$–$Cp_2Ti[P(OEt)_3]_2$ System] . . . 60
TABULAR SURVEY . . . 61
Table 1A. Homocoupling of Aldehydes . . . 62
Table 1B. Homocoupling of Ketones . . . 127
Table 1C. Homocoupling of Miscellaneous Compounds . . . 212
Table 2A. Mixed-Coupling of Aldehydes . . . 215
Table 2B. Mixed-Coupling of Ketones . . . 219
Table 2C. Mixed-Coupling of Aldehydes and Ketones . . . 277
Table 2D. Mixed-Coupling between Ketones and Carboxylic Acid Derivatives . 294
Table 3A. Intramolecular Coupling of Dialdehydes . . . 300
Table 3B. Intramolecular Coupling of Diketones . . . 340
Table 3C. Intramolecular Coupling of Keto Aldehydes . . . 369
Table 3D. Intramolecular Coupling of Oxo Esters, Oxo Amides, and Related Compounds 388
Table 4A. Tandem Homocoupling . . . 416
Table 4B. Tandem Mixed-Coupling . . . 449
REFERENCES . . . 451

INTRODUCTION

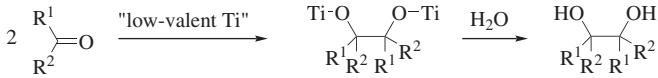
Reductive coupling of carbonyl compounds leading to pinacols or alkenes is a powerful synthetic transformation. The deoxygenative coupling of carbonyl compounds leading to the formation of alkenes is a rather newly developed synthetic method relative to other transformations such as the classical pinacol coupling. In 1970 Schreibmann first reported the formation of alkenes as minor products in the pinacol coupling of aromatic carbonyl compounds with aluminum amalgam.[1] The reductive coupling of both aromatic and aliphatic aldehydes and ketones using low-valent tungsten species generated by treatment of WCl_6 with two equivalents of BuLi was described shortly thereafter.[2] Although the process remains inefficient for the preparation of aliphatic alkenes, it works well to provide various stilbenes. The seminal deoxygenative carbonyl coupling with highly oxophilic titanium species was reported independently in 1973 and 1974 by Mukaiyama,[3] Tyrlik,[4] and McMurry.[5] The $TiCl_3$–$LiAlH_4$ system developed by McMurry was the first synthetically useful transformation of aliphatic carbonyl compounds into alkenes, demonstrating the versatility of the coupling system.

After four decades of study, a variety of low-valent titanium species have been found to promote the reductive coupling of a range of both aromatic and aliphatic aldehydes and ketones to furnish alkenes in inter- and intramolecular reactions (Scheme 1). Consequently, the McMurry coupling has been recognized as one of the most efficient methods for the synthesis of alkenes from carbonyl compounds.



Scheme 1

The initial studies shed light on the reagent- and substrate-dependence of reactivity. The concomitant or preferential formation of pinacols via titanium pinacolates, which are typically recognized as intermediates of the McMurry coupling, is observed in certain cases (Scheme 2). This chapter discusses the direct deoxygenative transformation of carbonyl compounds into alkenes and excludes the sequential formation of alkenes via pinacols and related compounds.



Scheme 2

The low-valent titanium reagents were initially prepared by the reduction of $TiCl_4$ or $TiCl_3$ with Zn dust or $LiAlH_4$. Further development of $TiCl_3(DME)_{1.5}$–Zn/Cu has improved yields and reproducibility, and extended the range of application.[6] More recent accounts describe highly active titanium reagents such as the $TiCl_3$–C_8K system,[7] permitting the intramolecular coupling of carboxylic acid derivatives with ketones or aldehydes. A variety of low-valent metal species other than titanium, including aluminum, zirconium, niobium, molybdenum, indium, tungsten, and samarium, have also been found to promote the reductive coupling of carbonyl compounds. Details of the low-valent metal reagents used in the McMurry coupling will be reviewed in the "Scope and Limitations" section.

Numerous synthetic applications of the coupling reaction, including the preparation of sterically congested and strained alkenes, as well as the formation of medium- and large-ring compounds, have been reported. In addition to these theoretically interesting alkenes, the preparation of biologically active targets and compounds useful in materials science using the McMurry coupling as a key step has been investigated extensively, and these results are summarized in the Tabular Survey. All these studies have been outlined in earlier reviews.[8–25]

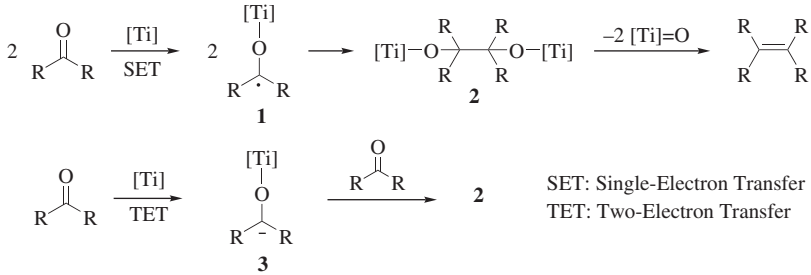
Despite the achievements described in this chapter, several challenges still remain in the deoxygenative coupling of carbonyl compounds. These include the control of double-bond geometry in the construction of highly substituted alkenes as well as the selective mixed-coupling of two distinct carbonyl compounds, particularly the intermolecular coupling of carboxylic acid derivatives. In this regard, the low-valent metal-mediated mixed-coupling of carbonyl equivalents such as thioacetals and *gem*-dihalides with various carbonyl compounds will be

briefly described in the "Scope and Limitations" section as carbonyl substitutes in the mixed McMurry coupling.

Recent theoretical studies suggest that the coupling follows alternative reaction pathways other than those involving pinacolate intermediates.[26] It is expected that the design of new low-valent metal reagents based on such theoretical insights into the McMurry coupling may provide solutions for the remaining problems.

MECHANISM

The reaction mechanism for the McMurry coupling remains unknown. Most mechanistic studies suggest that the reaction is composed of two processes: (1) formation of pinacolate intermediates **2**, and (2) deoxygenation of the pinacolates **2** leading to the formation of alkenes (Scheme 3).[26] When aliphatic ketones are employed, the formation of **2** is thought to proceed by the dimerization of ketyl radicals **1** by one-electron reduction of the carbonyl groups with low-valent titanium reagents. In the coupling of more active aromatic ketones, a two-electron reduction may take place to give dianions of ketones **3**, which then undergo nucleophilic addition to other ketones to furnish the pinacolate intermediates **2**.



Scheme 3

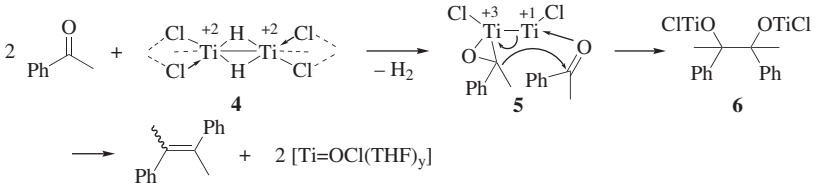
The mechanism composed of the above two distinct steps is supported by the observation that the pinacols may be isolated by carrying out the reaction at low temperature, whereas alkenes are produced at higher temperature using the same carbonyl coupling mediated by low-valent titanium reagents.[3,5] It has been proposed by McMurry that the pinacolate intermediates, coordinated to the same surface of a zero-valent titanium particle, but not to the same titanium atom, undergo stepwise cleavage of the C–O bonds and form the C=C bond.[27] Although the Ti–pinacolate intermediates could not be characterized because of the heterogeneous nature of the conditions, the pinacolate intermediates have been isolated in the reactions of carbonyl compounds with titanocene(III) dihalides[28] and titananorbornadiene complexes.[29]

The McMurry coupling is usually performed using inorganic low-valent titanium species, prepared in situ by reduction of titanium halides such as $TiCl_4$ or

$TiCl_3$ with various reductants. It has been assumed that finely dispersed particles of titanium are the active species in these reactions. However their oxidation states and structures have not been definitively identified. A zero-valent titanium species is proposed to be the active species in the coupling of ketones with the $TiCl_3$–Li, K, or Mg system,[30] and a mixture of Ti(0), Ti(I), and Ti(II) with the $TiCl_3$–$LiAlH_4$ system.[30] Conversely, it has been proposed that the McMurry coupling of ketones occurs on the ensemble of reduced titanium cations (+1, +2, and +3) on the TiO_2 (001) surface via the formation of pinacolate intermediates.[31]

The active species for the practical coupling using the $TiCl_3$–$LiAlH_4$ system has been isolated and characterized as $[HTiCl(THF)_{0.5}]_n$ (**4**) (Eq. 1).[32] That species possesses a chain-like structure composed of repeating units of dimeric or trimeric titanium atoms bridged through hydrogen. The titanium hydride **4**, which acts as a two-electron reductant, promotes the deoxygenative coupling of acetophenone to give 2,3-diphenyl-2-butene (Scheme 4).[33] As such, the reaction is thought to proceed through the formation of the ketone dianion intermediate **5** that is converted into pinacolate intermediate **6** by way of nucleophilic addition. In this regard, it is a prerequisite to reduce the $TiCl_3$ with $LiAlH_4$ completely before addition of carbonyl substrates.

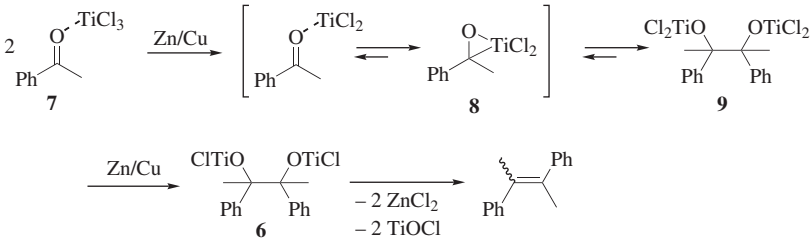
$$[TiCl_3(THF)_3]_n + 0.5n\ LiAlH_4 \longrightarrow [HTiCl(THF)_{0.5}]_n\ (\mathbf{4}) + 0.5n\ H_2 + 0.5n\ LiCl + 0.5n\ AlCl_3 \qquad \text{(Eq. 1)}$$



Scheme 4

When employing the $TiCl_3(DME)_{1.5}$–Zn/Cu system, the reduction of $TiCl_3$ with zinc takes place only in the presence of carbonyl substrates.[33] This observation indicates that no low-valent titanium species are formed in the absence of the carbonyl groups, and therefore, pre-reduction of the titanium halide prior to carbonyl addition is unnecessary. A proposed reaction mechanism for the McMurry coupling of acetophenone using this system is illustrated in Scheme 5.[33] The reaction is presumed to begin with the reduction of the acetophenone–$TiCl_3$ complex **7** with Zn/Cu by lowering the reduction potential of $TiCl_3$ through coordination to the Lewis basic oxygen. The "side-on" coordinated carbonyl complex of $TiCl_2$ **8**, a ketone dianion intermediate, is proposed as a precursor of the pinacolate **6**. The reduction of Ti^{3+} to Ti^{2+} by zinc is involved in both the conversion of the ketone to the pinacolate **9** and the pinacolate **9** to the alkene.

A similar mechanism involving the formation of ketone dianion intermediates like **8** by a two-electron transfer process has been proposed for the coupling of



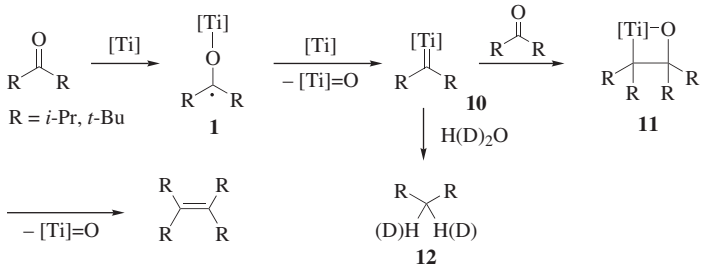
Scheme 5

aromatic ketones with $TiCl_2$, generated by the reaction of $TiCl_4$ with 2 equivalents of BuLi.[34] For the reactions in Schemes 4 and 5, the "side-on" coordinated carbonyl complex of $TiCl_2$ **8** is also proposed as a precursor for the pinacolates and, in the carbon–carbon bond formation step, the nucleophilic mechanism is operative rather than the radical mechanism. Ab initio calculations support the nucleophilic mechanism.[35]

By contrast, ketyl radical intermediates have been detected by ESR in the reductive coupling of aromatic ketones with the $TiCl_3$–Mg and $TiCl_3$–$LiAlH_4$ reagent systems.[30] The ketyl radicals on titanium complexes are also produced by the reaction of aliphatic ketones and aldehydes with $Ti(OSi\mathit{t}\text{-}Bu_3)_3$, generated by the reduction of $Ti(OSi\mathit{t}\text{-}Bu_3)_3Cl$ with Na(Hg). These have been characterized by ESR, although the radicals could not dimerize to form the pinacolates due to steric congestion.[36]

An alternative mechanism proposed for the McMurry coupling of hindered ketones involves titanium carbene intermediates rather than pinacolates. This hypothesis is supported by the observation that the pinacols are never obtained by the reductive coupling of diisopropyl ketone[37,38] and di-*tert*-butyl ketone[38,39] with the low-valent titanium species generated from the $TiCl_4$–Li/Hg system. Furthermore, it was demonstrated that the titanium pinacolates, $Cl_3TiOC(\mathit{i}\text{-}Pr)_2$–$(\mathit{i}\text{-}Pr)_2COTiCl_3$, prepared by transmetalation of the corresponding lithium pinacolate with $TiCl_4$, rapidly decomposes into diisopropyl ketone and $TiCl_3$ without formation of alkene.[37] These observations are consistent with the involvement of a titanium carbene mechanism in which the ketyl radicals **1,** formed by one-electron reduction of the ketones, undergo deoxygenative reduction to form the [Ti] intermediate **10**, probably due to steric hindrance (Scheme 6).[26] Intermediate **10** then reacts with the ketone to give the oxatitanacyclobutane intermediates **11** that lead to the formation of alkenes by metathesis-type degradation. When the reaction of di-*tert*-butyl ketone is quenched with D_2O, the dideuterated alkane **12** is produced, further supporting the presence of a titanium carbene intermediate.

In view of the similarities in structure and reactivity of uranium and titanium, the reductive coupling of ketones with uranium compounds has been investigated as model reactions to obtain more details about the mechanism of the McMurry coupling. The above-mentioned mechanism involving the pinacolate intermediates is supported by these studies. Thus, the uranium pinacolates of

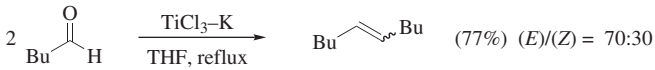


Scheme 6

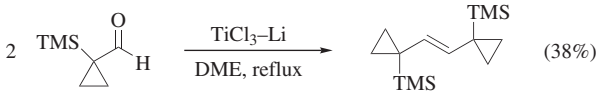
benzophenone[40] and acetone[41,42] have been isolated and characterized as intermediates, which undergo the deoxygenation to produce the corresponding alkenes upon heating the reaction mixtures at reflux temperatures.

STEREOCHEMISTRY

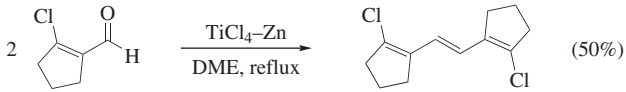
In general, the McMurry coupling of aldehydes and unsymmetrical ketones furnishes mixtures of (*E*)- and (*Z*)-isomers. The (*E*)/(*Z*) ratio is dependent on the reagents and structure of the substrates. The preferential formation of (*E*)-isomers is observed in the homocoupling of both aliphatic and aromatic aldehydes. The (*E*)/(*Z*) ratio of the alkene thus produced is improved with bulkier substituents. When pentanal is subjected to the coupling with the $TiCl_3$–K system, 5-decene is formed with a diastereomeric ratio of (*E*)/(*Z*) = 70:30 (Eq. 2).[27] By contrast, sterically hindered aldehydes such as cycloalkanecarbaldehydes (Eqs. 3 and 4)[43,44] and aromatic aldehydes afford only (*E*)-alkenes.



(Eq. 2)



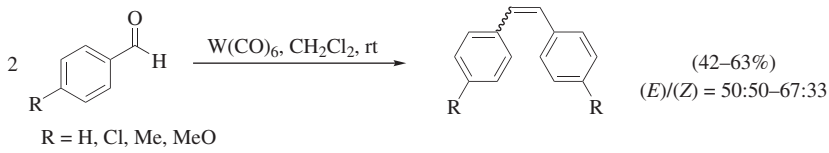
(Eq. 3)



(Eq. 4)

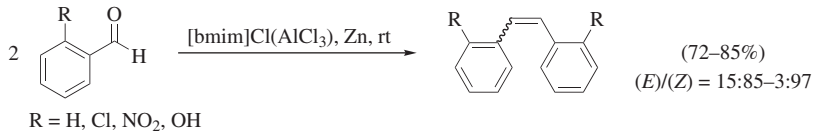
The (*E*)-selectivity is dramatically decreased when $W(CO)_6$ is employed in the reductive coupling of substituted benzaldehydes (Scheme 7).[45] It is proposed that the reaction proceeds through the formation of carbene intermediates generated by the reaction of low-valent tungsten with the aryl-substituted aldehyde.

By contrast, the homocoupling of aromatic aldehydes using the ionic liquid, 1-butyl-3-methylimidazolium chloroaluminate [bmim]$ClAlCl_3$ in combination with



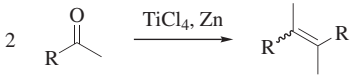
Scheme 7

zinc exhibits preferential formation of (*Z*)-stilbenes (Scheme 8),[46] although the reasons for this are not clear.



Scheme 8

The homocoupling of unsymmetrical aliphatic ketones generally affords (*E*)-alkenes. Increasing the size difference of the two alkyl groups improves the selectivity. As shown in Scheme 9, the coupling of methyl ethyl ketone with the $TiCl_4$–Zn–Py system furnishes an (*E*)/(*Z*) mixture of 3,4-dimethyl-3-hexene with a slight excess of the (*E*)-isomer, whereas only the (*E*)-alkene is formed by the coupling of *tert*-butyl methyl ketone under similar conditions.[47]

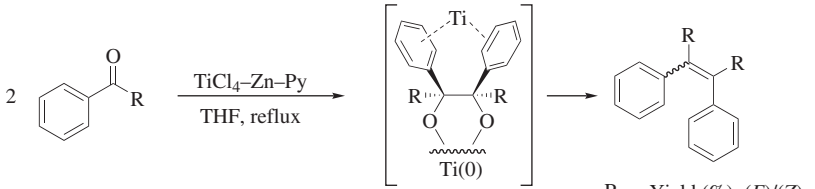


R	Yield (%)	(*E*)/(*Z*)
Et	65	1.1:1
Pr	61	1.4:1
i-Pr	46	1.5:1
neopentyl	48	100:0
t-Bu	62	100:0

Scheme 9

When sterically less encumbered alkyl aryl ketones, such as acetophenone, are subjected to the conventional McMurry coupling conditions, (*Z*)-stilbenes are preferentially obtained (Scheme 10).[48] This selectivity has been attributed to the complexation of the aromatic ring with titanium in the pinacolate intermediates **13**, in which the two phenyl rings adopt a *syn* configuration. The coupling of the sterically hindered isopropyl phenyl ketone results in preferential formation of the (*E*)-alkene.

A π–π pre-association of the aromatic rings in a transition state or at a pinacolate intermediate stage may also explain the (*Z*)-selective formation of

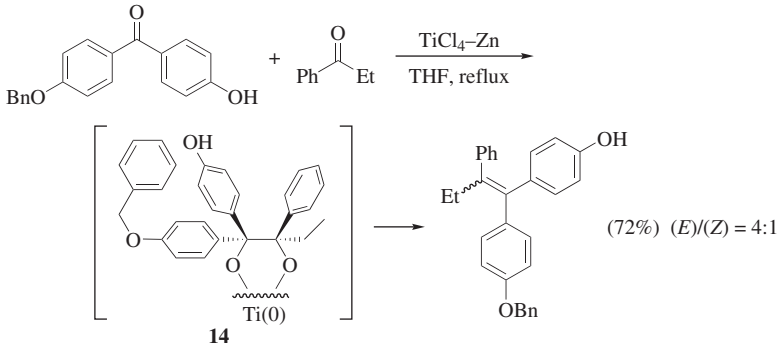


R	Yield (%)	(*E*)/(*Z*)
Me	81	26:74
Et	59	27:73
Pr	55	11:89
i-Pr	25	88:12

Scheme 10

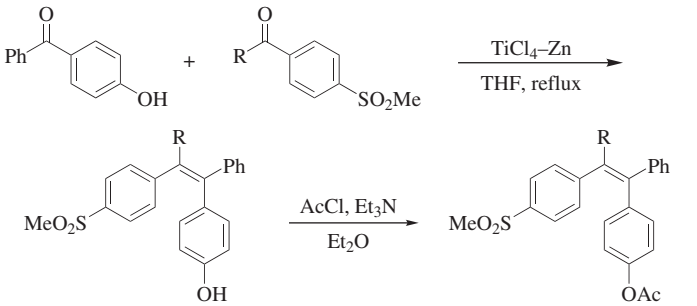
the stilbenes. Such a $\pi-\pi$ stacking interaction has also been suggested for the non-negligible formation of the (*Z*)-isomer in the coupling of large π-electron systems such as porphyrin[49]- and chlorin[50]-based aldehydes.

The stereoselectivity of the double bond formation by the mixed McMurry coupling is also affected by the steric demand of the substituents proximal to the carbonyl groups. The mixed-coupling of unsymmetrical 4,4′-disubstituted benzophenones with propiophenone generally exhibits (*E*)-selectivity when the sizes of the two substituents are significantly different.[51–55] For example, the reaction with 4-benzyloxy-4′-hydroxybenzophenone produces the corresponding alkene in an (*E*)/(*Z*) ratio of 4:1 (Scheme 11).[53] The observed selectivity can be ascribed to the pinacolate intermediate **14**. Because of steric hindrance, the phenyl ring bearing the larger substituent and the ethyl group are positioned on the same side to give (*E*)-alkenes. In contrast, the reaction of 4-benzyloxy-4′-perfluorotolyloxybenzophenone results in only a slightly higher (*E*)/(*Z*) ratio, because of a small difference in bulkiness of the two substituents. A substituent at the *ortho* position of a benzophenone significantly improves the (*E*)-selectivity in the McMurry coupling of propiophenone.[56]



Scheme 11

High levels of (*Z*)-selectivity have been achieved in the McMurry coupling between benzophenones and alkanophenones bearing hydroxyl and methylsulfonyl functionalities at the *para*-position of the arene ring of each coupling component. This outcome is obtained regardless of whether the alkanophenones possess a hydroxy or methylsulfonyl group.[57–59] For example, the mixed McMurry coupling between 4-methylsulfonylalkanophenones and 4-hydroxybenzophenone furnishes the triarylethenes with complete (*Z*)-selectivity (Scheme 12).[58] Less selective formation of (*Z*)-alkenes is observed in the reaction of *para*-acetoxy substituted alkanophenones with 4-methylsulfonylbenzophenone.[57]



R = H, Me, Et, Pr, n-C_5H_{11}, n-C_6H_{13}, n-C_9H_{19} (63–72%) >99% (*Z*)-isomer

Scheme 12

SCOPE AND LIMITATIONS

Coupling Reagents

Various low-valent metal reagents promote the reductive coupling of two carbonyl compounds to form alkenes.[60] Due to the oxophilicity of titanium, the most common reagents in the McMurry coupling are those prepared by the reduction of Ti(III) or Ti(IV) chlorides with a range of reducing agents ($LiAlH_4$, Li, Na, Mg, K, Zn, Zn/Cu). Depending on the reducing agents, additives, and conditions, various low-valent titanium species with different oxidation states and reactivities are generated. The most commonly used reagents are described below.

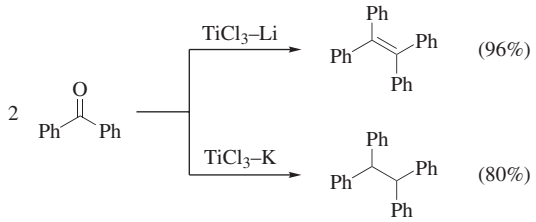
Low-Valent Titanium-Based Reagents

The $TiCl_4$–Zn System. The $TiCl_4$–Zn system couples aromatic aldehydes and ketones at elevated temperature to furnish substituted alkenes. Heat is essential because the treatment of these compounds with low-valent titanium species at ambient temperature results in the exclusive formation of pinacol derivatives.[3] Similar treatment of aliphatic carbonyl compounds produces only pinacols, even at higher temperature. Several modified reagent systems, such as $TiCl_4$–Zn/Cu, $TiCl_4$–Zn–CuCl, and $TiCl_4$–Zn–CuI, are also employed for the McMurry coupling.

The $TiCl_3$–Zn/Cu System. The $TiCl_3$–Zn/Cu system was first employed for the intramolecular coupling of aliphatic as well as aromatic diketones.[61] This reagent is a safer and more effective alternative to low-valent titanium reagents generated by reduction with either potassium or lithium reagents (see below). An optimized procedure for the preparation of this reagent involves the reduction of $TiCl_3(DME)_{1.5}$ with a Zn/Cu couple. The low-valent titanium species thus formed is one of the most widely used low-valent titanium reagents.[6] An additional advantage of this procedure is that $TiCl_3(DME)_{1.5}$ is stable and may be purified by crystallization.

The $TiCl_3$–$LiAlH_4$ System. The $TiCl_3$–$LiAlH_4$ system was first employed by McMurry to carry out the deoxygenative coupling of both saturated and unsaturated ketones. The reagent can be employed for the preparation of β-carotene from retinal.[5] The procedure remains problematic such that successful results seem to be dependent on the specific batches of reagent used.[62] However, the intramolecular coupling of oxo esters is readily performed with the $TiCl_3$–$LiAlH_4$ system in the presence of triethylamine.[63]

The $TiCl_3$–Alkali or Alkaline Earth Metal System. The low-valent titanium reagent generated by the reduction of $TiCl_3$ with potassium metal according to Rieke's procedure[64] is a good alternative to the $TiCl_3$–$LiAlH_4$ system for the coupling of saturated aliphatic ketones.[62] To avoid the use of hazardous potassium for the preparation of low-valent titanium species, an improved procedure using lithium metal was developed. The reagent thus formed is equally effective for the deoxygenative coupling of a variety of carbonyl compounds in both inter- and intramolecular reactions. A difference between the two reagents is shown in Scheme 13: the titanium reagent prepared by the reduction of $TiCl_3$ with lithium affords tetraphenylethylene in high yield whereas the similar reaction using the $TiCl_3$–K system results in the formation of tetraphenylethane.[27]



Scheme 13

One of the earliest studies on deoxygenative coupling employed the $TiCl_3$–Mg system that promotes the coupling of both aliphatic and aromatic ketones. Despite further studies on this reagent,[3,65,66] only limited applications for the McMurry coupling have been reported.

The $TiCl_3$–Lithium Arene System. The preparation of low-valent titanium reagents by the reduction of $TiCl_3$ with Li–arenes has been investigated and the study reveals that the reagent prepared by using the Li–naphthalene combination is reactive enough to carry out the transformation of carbonyl compounds into alkenes under milder conditions as compared with the conventional $TiCl_3$–Li system.[67]

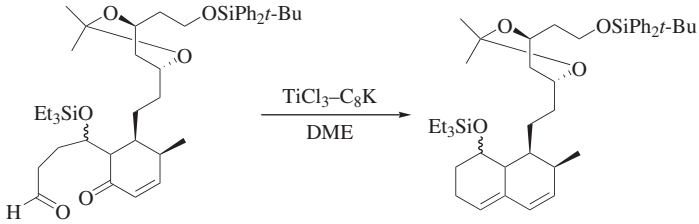
The $TiCl_4$–BuLi System. Treatment of $TiCl_4$ with two equivalents of BuLi in THF produces an isolable, and well-characterized, divalent titanium species (Eq. 5).[34] This reagent promotes the reductive coupling of aromatic aldehydes and ketones to form the corresponding (*E*)-alkenes with high levels of stereoselectivity. A similar reagent generated from TiF_4 is also capable of promoting the same coupling reaction.[68]

$$TiCl_4 + 2\,BuLi \xrightarrow[-\,2\,LiCl]{THF} TiCl_2(THF)_2 + BuH + EtCH{=}CH_2 \qquad \text{(Eq. 5)}$$

Supported Titanium Reagents. A major disadvantage of the $TiCl_3$–alkali metal system is the low efficacy and the need for the use of pyrophoric reducing agents. By contrast, sodium deposited on inorganic supports such as Al_2O_3, TiO_2, or NaCl are readily available nonpyrophoric reducing agents for $TiCl_3$.[69] Consequently, these reagents are useful for the inter- and intramolecular McMurry coupling of aromatic carbonyl compounds. Both the inter- and intramolecular coupling reactions of acyltrimethylsilanes were first realized by the use of these reagents.[70]

The intercalation compound potassium in graphite (C_8K) acts as a powerful reducing agent toward transition-metal halides dissolved or suspended in THF.[71] The low-valent titanium generated by the reduction of $TiCl_3$ with C_8K is highly useful for all types of McMurry coupling reactions,[72–77] including the intramolecular reaction of oxo amides.[7,78–83] The $TiCl_3/C_8K$ ratio is crucial for the preparation of a highly activated form of titanium. Although the initially reported titanium reagent generated by the reduction of $TiCl_3$ with three equivalents of C_8K (formally a Ti(0) species) is successfully employed for the various coupling processes, the reagent generated by the reduction of $TiCl_3$ with two equivalents of C_8K (formally a Ti(+1) species) is much more reactive and provides more reproducible results for the cyclization of the keto aldehyde shown in Scheme 14.[84]

Titanium Powder. Commercial titanium powder exhibits exceptional resistance to chemical attack. The treatment of titanium powder with TMSCl in boiling THF or DME for dozens of hours removes a thin oxide layer on its surface and the activated Ti(0) species can be employed for the McMurry coupling. The reagent effectively promotes the coupling reactions of aromatic and α,β-unsaturated aldehydes or ketones as well as the intramolecular mixed-coupling leading to aromatic heterocyclic compounds.[83,85] However, aliphatic carbonyl compounds are not good substrates for this reagent.



$TiCl_3/C_8K$	Substrate/$TiCl_3$	Yield (%)
1.00:4.07	1.00:10.00	0
1.00:3.00	1.00:10.00	30
1.00:2.09	1.00:17.14	85

Scheme 14

Other Titanium-Based Reagents. Several well-defined low-valent titanium species are known to promote the deoxygenative coupling of carbonyl compounds. The reductive coupling of aromatic aldehydes and ketones with $Cp_2Ti(CO)_2$ produces alkenes along with the corresponding pinacols.[86] For example, the intramolecular coupling of 2-(benzoylamino)benzophenone is promoted with the Ti(0) species such as electrochemically generated Ti-clusters, $Ti(PhMe)_2$, and $Ti(biphenyl)_2$, as well as the Ti(II) compound $Cp_2Ti(PMe_3)_2$.[7] The treatment of aromatic aldehydes and acetophenone with the reagent system $Ti(O\textit{i}\text{-}Pr)_4$–TMSCl–Mg–$Et_3N$ affords the McMurry coupling products.[87]

Low-Valent Metals Other Than Titanium

Aluminum and Zinc Reagents. The reagent generated by the treatment of $AlCl_3$ with zinc promotes the coupling of aromatic and aliphatic aldehydes and ketones with (*E*)-stereoselectivity at reflux in MeCN.[88] Conversely, the treatment of benzophenone derivatives with the $AlCl_3$–Zn system in MeCN at 35° under ultrasonic irradiation results in the exclusive formation of benzopinacolones via reductive coupling–rearrangement, except for some bridged benzophenones such as xanthone.[89]

In certain cases, zinc alone promotes the deoxygenative coupling of carbonyl compounds. The treatment of steroidal conjugated dienones with zinc dust activated by HCl in THF under reflux affords the desired deoxygenative coupling products.[90] The reagent system Zn–TMSCl can be applied to both the coupling of aryl and α,β-unsaturated carbonyl compounds to alkenes,[91] and the McMurry-type coupling of metallocenyl ketones. A very low concentration of HCl must be present to obtain satisfactory results.[92] Zinc dust in combination with the acidic ionic liquid 1-butyl-3-methylimidazolium chloroaluminate converts aromatic aldehydes and ketones to alkenes with (*Z*)-stereoselectivity.[46]

Zirconium Reagents. Similarly to titanium, the low-valent zirconium reagent generated by the reduction of $ZrCl_4$ with lithium reacts with aromatic

aldehydes and ketones to produce alkenes with (*E*)-stereoselectivity. Bicyclohexylidene is obtained in moderate yield by the reaction of cyclohexanone using this procedure.[93]

Vanadium and Niobium Reagents. The treatment of 9-fluorenone with VCl affords the deoxygenative coupling product in quantitative yields although its use for the McMurry-type coupling is largely restricted.[94] The active niobium reagent generated by the reduction of $NbCl_5$ with $NaAlH_4$ is effective for the coupling of aromatic aldehydes and ketones to produce arylethenes. 2-Heptanone is transformed into 6,7-dimethyl-6-dodecene by treatment with this reagent but in moderate yield.[95] The reduction of $NbCl_5$ with one equivalent of MeLi or metallic potassium gives an active low-valent niobium reagent which reacts with aromatic carbonyl compounds to give the corresponding alkenes. The $NbCl_5$–K system is more reactive than $NbCl_5$–MeLi and it transforms cycloheptanone into the dimerized alkene in good yield.[96] (Arene)tricarbonylchromium ketones undergo reductive coupling to produce mixtures of mono- and di-metallated alkenes when treated with $NbCl_3$(DME). Mono-metallated alkenes are obtained exclusively by the similar reaction of (arene)tricarbonylchromium aldehydes.[97]

Molybdenum and Tungsten Reagents. $Mo(CO)_6$[45] and $W(CO)_6$[45,98] promote the deoxygenative coupling of benzaldehyde in appropriate solvents but the yields are only moderate. The low-valent tungsten reagent generated by the reduction of WCl_6 with BuLi mediates the coupling of aromatic carbonyl compounds.[2] This reagent also performs the coupling of aliphatic carbonyl compounds, albeit with lower efficiency. Similar results are also obtained by taking advantage of the reagent prepared by treatment of WCl_6 with $LiAlH_4$.[45] Various aromatic and aliphatic aldehydes and ketones are transformed into alkenes by treatment with ditungsten hexaalkoxides such as $W_2(OCH_2CMe_3)_6Py_2$.[99,100] The reaction proceeds via the initial formation of tungsten alkylidene-bridged intermediates.[101,102] The reagent produced by electrochemical reduction of WCl_6 promotes the coupling of aromatic carbonyl compounds but it cannot be used for the reductive coupling of aliphatic counterparts.[103]

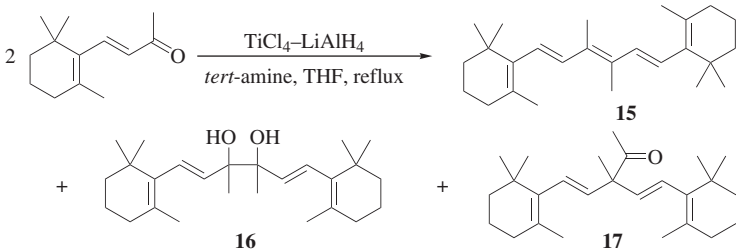
Indium Reagents. The system $InCl_3$–Zn reductively couples aromatic and aliphatic aldehydes and aromatic ketones in MeCN at ambient temperature with (*E*)-stereoselectivity.[104]

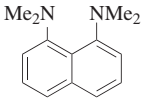
Samarium and Ytterbium Reagents. Although the deoxygenative coupling of two carboxylic acid derivatives is not achieved by the conventional McMurry coupling, *vic*-diaminoalkenes are obtained by the treatment of amides with the Sm–SmI_2 system.[105] However, with some amides bearing a double bond at an appropriate position, the major course of the reaction is cyclopropanation of the double bond. The system can be applied to the intermolecular coupling between aromatic amides and diaryl ketones.[106] The SmI_2–Mg system is also employed for the same intermolecular coupling.[107] The Yb–YbI_2 system shows similar reactivity to the Sm–SmI_2 system and can be applied to the coupling of amides.[108]

Uranium and Thorium Reagents. The reduction of UCl_4 with $[(TMEDA)Li]_2[Np]$ affords a highly reactive uranium metal powder that produces tetraphenylethylene in moderate yield on treatment with benzophenone.[17] The deoxygenative coupling of benzophenone is also observed, but in lower yield, when treated with thorium metal powder prepared similarly. Another method for the preparation of highly reactive uranium powder is the reduction of UCl_4 with Na–K alloy and 5–10% naphthalene. The reagent also converts benzophenone to tetraphenylethylene in refluxing DME.[109]

Effect of Additives

In general, the McMurry coupling is performed with a titanium source and a reducing agent in an appropriate solvent. In certain cases, the use of additives greatly improves the reactivity of the reagents. The effect of amines for the selective formation of alkenes was first reported by Mukaiyama.[110] In the coupling of β-ionone using the $TiCl_4$–$LiAlH_4$ system, the addition of tertiary amines enhances the yield of alkene **15** by suppressing the concomitant formation of pinacol **16** and its rearrangement product **17** (Scheme 15).[110]



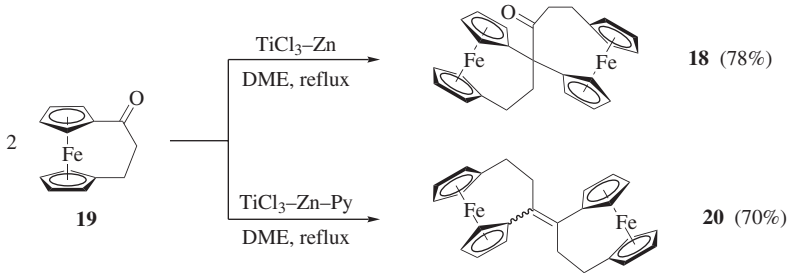
tert-Amine	**15** (%)	**16** (%)	**17** (%)
none	44	8	25
Bu_3N	91	0	0
Py	82	0	0
Et_3N	82	0	0
	94	0	0
DABCO	72	0	0

Scheme 15

The $TiCl_4$–Zn system also benefits from addition of pyridine. In its absence, reductive coupling of aliphatic ketones affords the pinacol coupling products exclusively,[3] whereas tetrasubstituted ethenes are produced when the reactions are run in the presence of pyridine.[111] The system $TiCl_4$–Zn–Py is one of the most widely used reagents for the McMurry coupling.

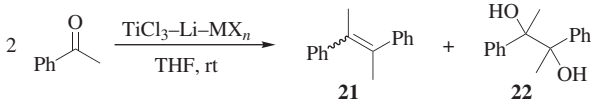
Another example of the suppression of pinacol rearrangement products is observed in the deoxygenative coupling using the $TiCl_3$–Zn system. Although

the reaction of ferrocenyl ketone **19** with this system results in the exclusive formation of the rearranged product **18**, the alkene **20** is selectively produced when pyridine is added (Scheme 16).[112] The intramolecular McMurry coupling of oxo esters by the $TiCl_3$–$LiAlH_4$ system is carried out in the presence of triethylamine.[63]



Scheme 16

Addition of Group 1 and 2 metal salts enhances the selectivity of the $TiCl_3$–Li system. The reductive coupling of acetophenone with the $TiCl_3$–Li system produces predominantly the pinacol **22**, but the combined use of KCl with the reagent system results in the exclusive formation of stilbene **21** (Scheme 17).[113,114]



MX_n	**21** (%)	**22** (%)
none	trace	89
$MgCl_2$	25	62
LiI	trace	75
CsCl	65	—
KCl	82	—
$ZnCl_2$	32	45

Scheme 17

Alternatively, activation of the $TiCl_3$–Li system is achieved by adding substoichiometric amounts of iodine. Although the conventional McMurry coupling with this system requires high temperatures and prolonged reaction times, the low-valent titanium species activated with iodine effects the deoxygenative coupling of aliphatic as well as aromatic carbonyl compounds at lower temperatures and in much reduced reaction times.[115]

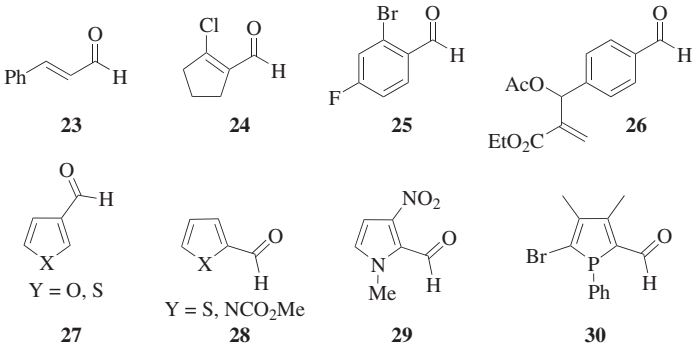
The Carbonyl Substrate

Although nearly all types of aldehydes and ketones are good substrates for the McMurry coupling, certain functional groups are not compatible with the reaction conditions as low-valent titanium species are highly reactive reducing agents. It is well known that the aqueous Ti(III) species are employed for the reductive

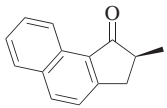
conversion of various organic compounds such as nitroalkanes, quinones, oximes, enedicarbonyl compounds, and α-halo ketones.[116] The reagent prepared by the reduction of $TiCl_3$ with $LiAlH_4$ converts epoxides and bromohydrins to alkenes, and allylic and benzylic alcohols are deoxygenated.[117] This reagent also reduces pinacol-containing compounds[27] as well as 2-ene-1,4-diols.[118] The reagent generated by the reduction of $TiCl_4$ with two equivalents of $LiAlH_4$ reduces acetals, thioacetals, sulfides, β-hydroxy sulfides, aryl halides, and alkenyl chlorides.[119] Various aromatic compounds, such as benzoic acid derivatives, halobenzenes, nitrobenzene, and diphenylacetylene, are also reduced by the low-valent titanium species generated under the reaction conditions.[120] β-Hydroxy sulfides and their benzoates are reductively transformed into alkenes by $TiCl_4$–Zn–Py systems.[119] Despite the possible reduction of functional groups under the McMurry conditions described above, aldehydes and ketones bearing such functional groups have been successfully employed for the McMurry coupling.

Relative to aldehydes and ketones, carboxylic acid derivatives are generally not effective substrates for the intermolecular McMurry coupling, and only a few examples of mixed-coupling between esters and ketones have been reported. Conversely, the intramolecular mixed-coupling of esters and amides with aldehydes and ketones is a useful method for the preparation of heterocyclic compounds. The homocoupling of amides is successfully achieved with Sm-based reagents.

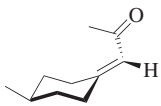
Aldehydes. The McMurry homocoupling of unsaturated aldehydes, such as cinnamaldehyde (**23**), with the $TiCl_4$–Zn–Py system proceeds with complete retention of configuration of the double bond.[121] Haloaldehydes **24**[5] and **25**[122] are coupled without reduction of the halogens using the $TiCl_4$–Zn system. The reaction of benzaldehyde **26** bearing ester and allylic acetate moieties with $TiCl_4$–Zn proceeds in good yield.[123] Most heterocycles, such as furan, thiophene, pyrrole, and pyridine, are compatible irrespective of the position of the formyl group as exemplified with **27** and **28**.[124] Even the pyrrole **29** bearing a nitro group is converted into the coupling product when treated with $TiCl_4$–Zn, albeit with unsatisfactory yields.[125] The bromophospholecarbaldehyde **30** is also successfully transformed into the phosphole-substituted ethene by the $TiCl_4$–Zn system-promoted coupling without loss of bromine.[126]



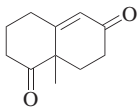
Ketones. Aliphatic, aromatic, α,β-unsaturated, acyclic, and cyclic ketones can be submitted to the McMurry conditions. Sterically congested ketones are transformed into the corresponding strained alkenes. The coupling of chiral α-substituted ketones such as **31** using the $TiCl_3$–$LiAlH_4$ system proceeds without epimerization.[127] The enantiomerically enriched enone **32** reacts with acetone in the presence of $TiCl_4$–$LiAlH_4$ to furnish the tetrasubstituted alkene without double bond isomerization.[128] Of note, the treatment of enone **33**[129] and dienone **34**[83] with the $TiCl_4$–Zn or Ti powder–TMSCl system results in the selective coupling of the unsaturated carbonyl groups. In addition to halogens, sulfonyl groups are compatible with the McMurry conditions as indicated in the coupling of 4-methylsulfonylacetophenone (**35**).[58] The reaction of the dienone **36** demonstrates the tolerance of both cyano and nitro groups.[130] Acylsilanes such as **37** react with $TiCl_3$–Na/Al_2O_3 to produce 1,2-disilylethene derivatives with (*E*)-stereoselectivity.[70,131] Acyltrimethylsilane **37** also reacts with 9-fluorenone in the presence of ytterbium to form the corresponding alkenylsilane.[132]



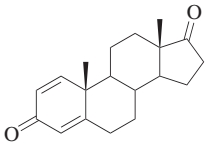
31



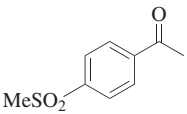
32



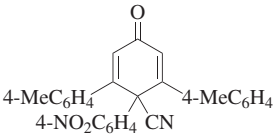
33



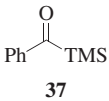
34



35

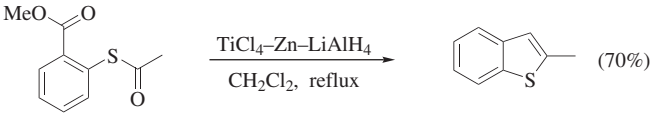


36



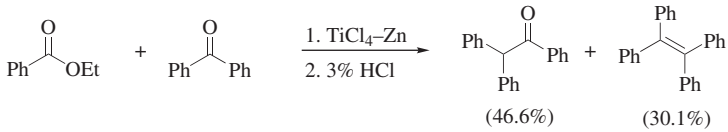
37

Esters. To date, the deoxygenative coupling between two esters has not been reported. Benzothiophenes may be prepared via the intramolecular reaction of an ester with thioester groups with the reagent generated from $TiCl_4$, Zn, and $LiAlH_4$ (Eq. 6).[133]

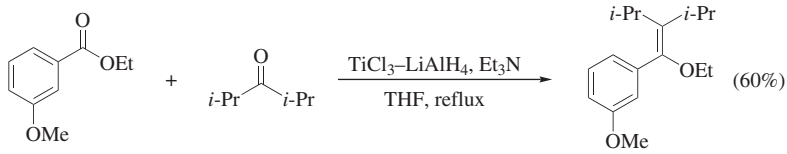


(Eq. 6)

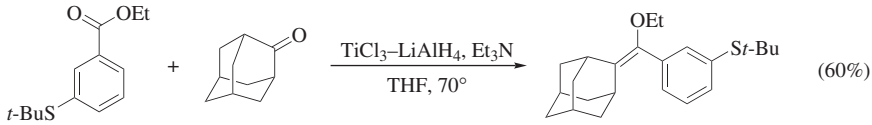
The intermolecular mixed-coupling of esters is possible with other carbonyl-containing compounds. Ketones are suitable partners in certain cases, although the homocoupling of ketones is always a side reaction; some examples are shown in Eqs. 7[134] and 8.[135] In this context, it is noteworthy that the reaction of ethyl 3-(*tert*-butylthio)benzoate with 2-adamantanone proceeds without formation of any homocoupling product (Eq. 9).[136]



(Eq. 7)

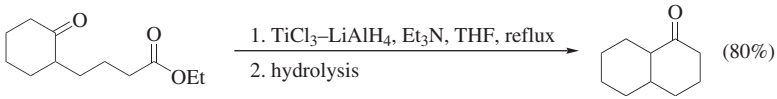


(Eq. 8)

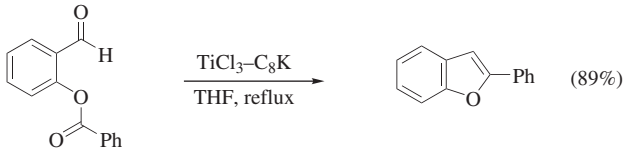


(Eq. 9)

Many intramolecular coupling reactions of esters with aldehydes and ketones have been studied. These reactions are useful and convenient for the preparation of a variety of cyclic ketones and furans (Eqs. 10[63] and 11[79]).

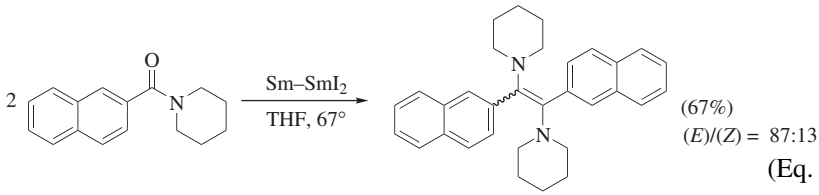


(Eq. 10)

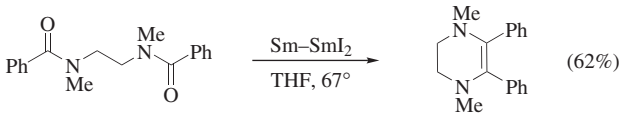


(Eq. 11)

Amides. The deoxygenative homocoupling of amides is performed by using the Sm–SmI_2 system. Both inter- and intramolecular processes have been delineated (Eqs. 12 and 13).[105] However, the yield decreases when aliphatic amides such as *N*,*N*-diethylpentanamide are employed.

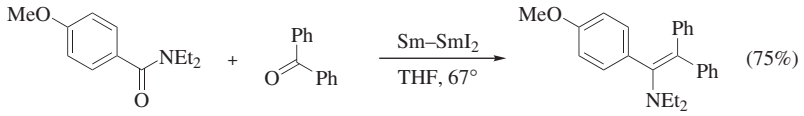


(Eq. 12)



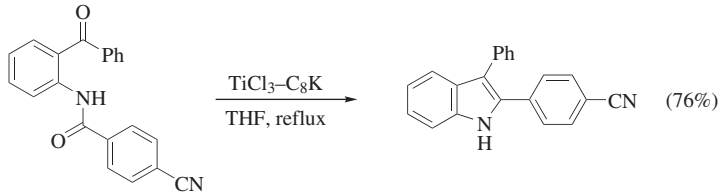
(Eq. 13)

The intermolecular, deoxygenative mixed-coupling between aromatic amides and benzophenone derivatives is promoted with the samarium-based systems, $Sm-SmI_2$[106] and SmI_2-Mg,[107] as shown in Eq. 14.[106]



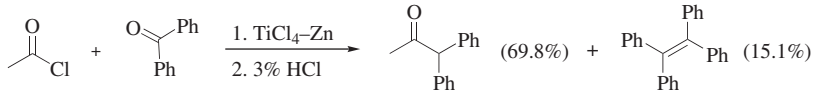
(Eq. 14)

The intramolecular coupling between amides and ketones has been extensively studied as a useful synthetic method for the preparation of various indole derivatives (Eq. 15).[79]

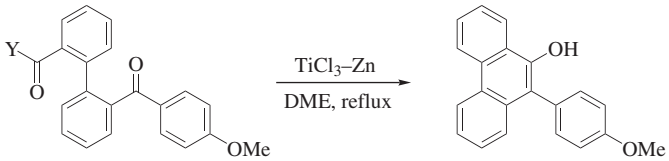


(Eq. 15)

Carboxylic Acids and Acid Halides. Only limited examples of the McMurry coupling of carboxylic acids and acyl halides are known. The $TiCl_4-Zn$ system-promoted intermolecular mixed-coupling of acetyl chlorides with benzophenone affords the corresponding ketones following acidic hydrolysis (Eq. 16).[134] The intramolecular reactions of benzoic acid and benzoic acid fluoride with the benzophenone moiety result in the formation of the corresponding phenols (Eq. 17).[137] It is suggested that the cleavage of the C–F bond in the latter reaction is the result of reductive elimination from the pinacolate intermediate during the coupling reaction.



(Eq. 16)

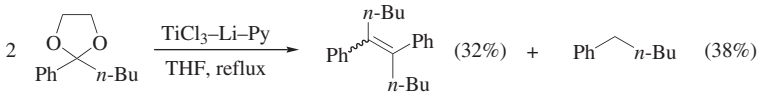


Y	Yield (%)
HO	86
F	90

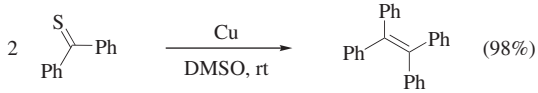
(Eq. 17)

Related Substrates. Benzylidene acetals are transformed into 1,2-diphenylethene derivatives under McMurry conditions. The yields are generally moderate due to the concomitant formation of arylalkanes (Eq. 18).[138] Treatment of

thiobenzophenone with copper powder in DMSO produces tetraphenylethylene (Eq. 19).[139] The desulfurizative coupling of thiobenzoylpiperidine and selenobenzoylpiperidine forming 1,2-dipiperidinostilbene is achieved with the Sm–SmI_2 system.[108]



(Eq. 18)



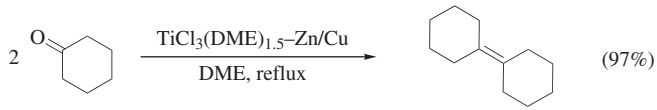
(Eq. 19)

Mode of Coupling of Aldehydes and Ketones

Flexibility makes the McMurry coupling a useful method for the construction of a range of carbon skeletons. Except for intermolecular homocoupling, this process suffers from a narrow substrate scope and, particularly in intramolecular coupling and tandem cyclizations, the yields vary widely depending on the substitution of the substrates. The judicious choice of reaction conditions for a given mode of reaction is also of crucial importance for a successful McMurry coupling.

Homocoupling. Because of the highly oxophilic nature of titanium species, a range of aldehydes and ketones can be employed in homocoupling, which serves as a useful method for the preparation of symmetrical alkenes. Both aromatic and aliphatic cyclic and acyclic carbonyl compounds are good substrates for homocoupling reactions (Eqs. 20[3] and 21[140]).

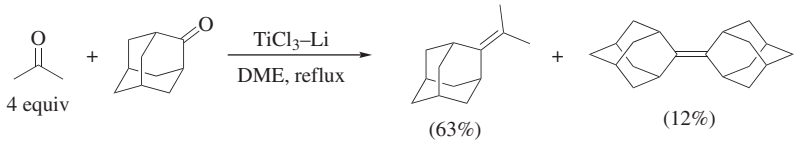
(Eq. 20)



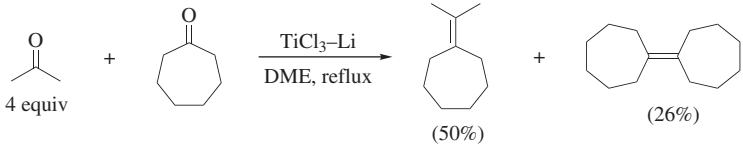
(Eq. 21)

Mixed-Coupling. In general, the mixed-coupling of two carbonyl compounds produces a nearly statistical mixture of the mixed and two possible homocoupling products. Therefore, use of one of the coupling components in excess is often necessary to obtain reasonable yields of the mixed-coupling products. This approach is particularly useful when volatile and inexpensive ketones such as acetone are employed. For example, the mixed-coupling of adamantanone with excess acetone affords isopropylideneadamantane in good yield (Eq. 22).[27] The success of mixed-coupling is also dependent on the structure of the ketones. In the mixed-coupling of cycloheptanone, a considerable amount of homocoupling product is formed even when an excess amount of acetone is used (Eq. 23).[27] Conversely, a similar reaction of benzophenone predominantly gives the mixed-coupling product (Eq. 24).[27] The preferential formation of the

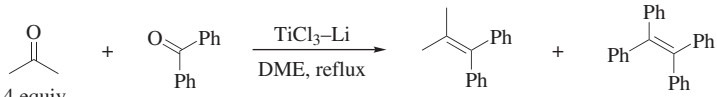
mixed-coupling product is explained by the formation of a dianion species by the two-electron reduction of benzophenone, whose reduction potential is 1.0–1.5 V less negative than that of acetone (Scheme 18).[141]



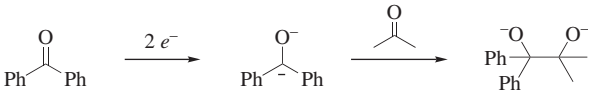
(Eq. 22)



(Eq. 23)

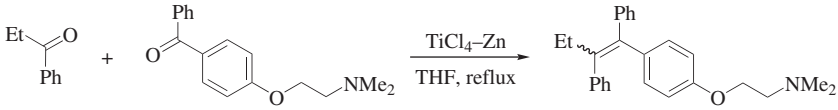


(Eq. 24)



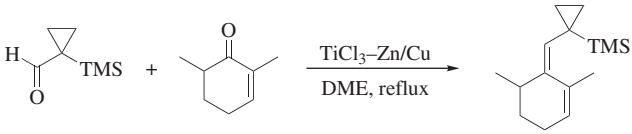
Scheme 18

Similar preferential formation of heterocoupled products is observed in the mixed-coupling of equimolar amounts of diaryl (Eq. 25)[142] or α,β-unsaturated ketones (Eq. 26)[143] with monoaryl ketones or their corresponding aliphatic counterparts. The success of these reactions is also attributable to the sufficiently different redox potentials of two coupling components.



(88%) (*E*)/(*Z*) = 1:3

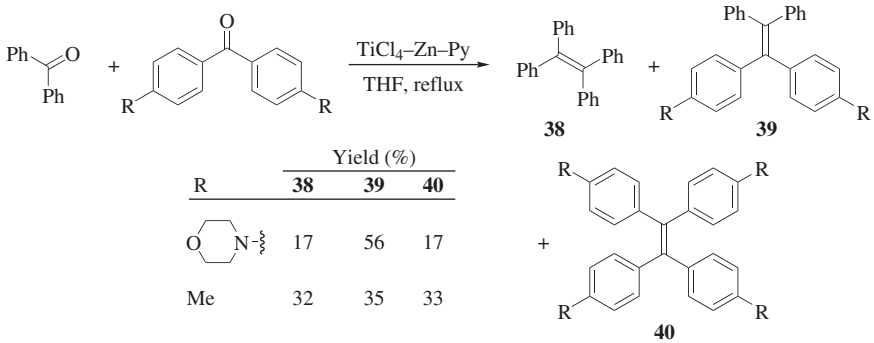
(Eq. 25)



(60%) (Eq. 26)

The preferential formation of mixed-coupling products is also observed when nitrogen- or oxygen-containing aryl or diaryl ketones are employed as one of the coupling components. Thus the reaction of benzophenone with an equimolar

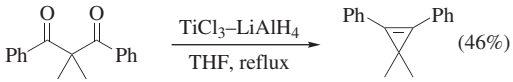
amount of 4,4′-dimorpholinobenzophenone yields the mixed-coupling product in a yield better than that expected from statistical probability whereas its reaction with 4,4′-dimethylbenzophenone affords no such selectivity as shown by the distribution of products **38**–**40** (Eq. 27).[144,145] It is believed that the strong affinity of the heteroatom substituents for the low-valent titanium surface is important for good selectivity.



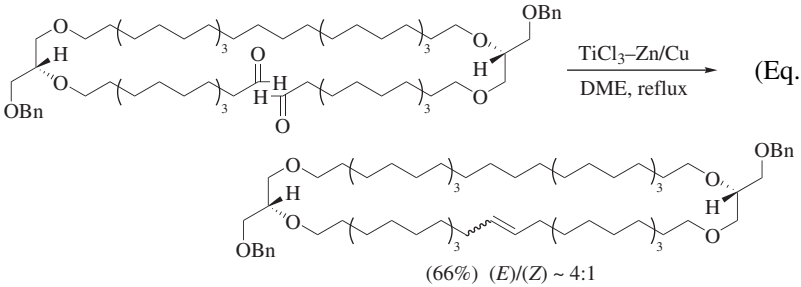
R	Yield (%) 38	39	40
	17	56	17
Me	32	35	33

(Eq. 27)

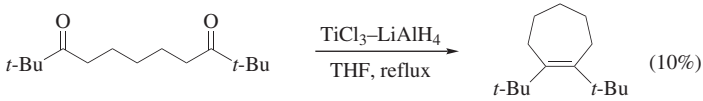
Intramolecular Coupling. A variety of intramolecular deoxygenative coupling reactions of aldehydes and ketones have been studied as useful methods for the construction of cyclic and macrocyclic compounds. Three (Eq. 28[146]) to 72-membered ring derivatives (Eq. 29[147]) have been synthesized to date. The McMurry coupling is particularly effective for the preparation of medium-size rings (Eqs. 30[148] and 31[61]).



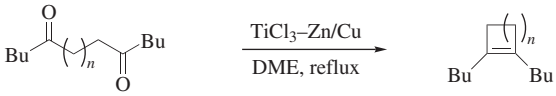
(Eq. 28)



(Eq. 29)



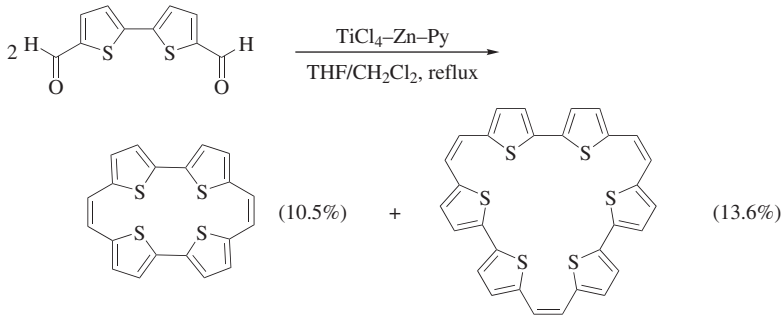
(Eq. 30)



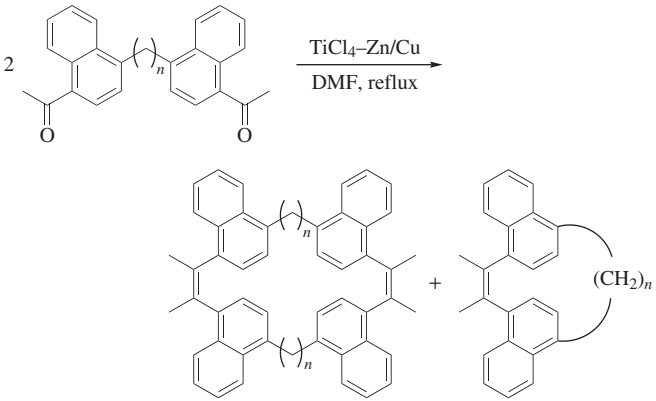
n	Yield (%)
5	67
6	68

(Eq. 31)

Tandem Cyclizations (Annulations). The tandem cyclization reaction consists of initial intermolecular coupling followed by subsequent intramolecular coupling. For the selective formation of cyclic dimers, a significant side reaction is the oligomerization of starting materials, as exemplified in Eq. 32.[149] In certain cases, the mode of the reaction is dependent on the distance between the two carbonyl groups. The exclusive formation of dimer **41** over intramolecular coupling product **42** is observed when the tether connecting the two 1′-acetonaphthone moieties contains one or two carbons, whereas the intramolecular coupling proceeds selectively if the carbon number is three (Eq. 33).[150]



(Eq. 32)

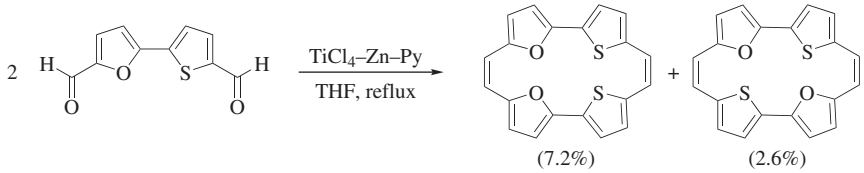


(Eq. 33)

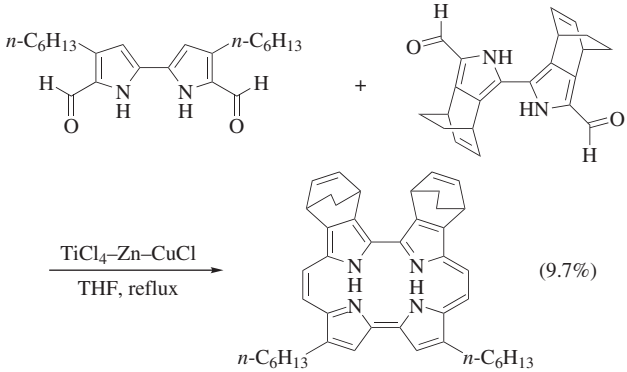
	Yield (%)	
n	**41**	**42**
1	64	—
2	40	—
3	trace	41

In the reaction of unsymmetrical dicarbonyl compounds, constitutional isomers should be formed (Eq. 34).[151] The tandem cyclization of two distinct dicarbonyl

compounds has also been investigated (Eq. 35).[152]



(Eq. 34)

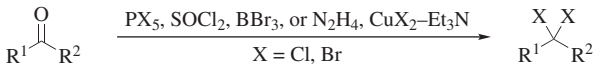


(Eq. 35)

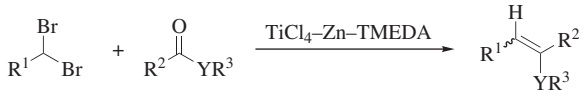
Related Reactions

Although the McMurry coupling is a versatile tool for the preparation of unsaturated compounds, several limitations arise in applying it to the mixed-coupling of two different carbonyl compounds. A major drawback is that the selective mixed-coupling between ketones and aldehydes is generally difficult to achieve in useful yields. The mixed-coupling of ketones or aldehydes with carboxylic acid derivatives is also largely restricted. Although the intramolecular coupling of carboxylic acid derivatives such as esters and amides is a useful route to heteroatom-substituted alkenes and heterocyclic compounds, only a limited number of examples of the intermolecular McMurry coupling using carboxylic acid derivatives as one of the coupling components are known (see Table 2D). In such cases, the low-valent titanium-promoted reactions of carbonyl compounds with various carbonyl equivalents such as *gem*-dihalides and thioacetals are useful complements to the mixed McMurry coupling.

Carbonyl Olefination with *gem*-Dihalides. Carbonyl compounds are transformed into *gem*-dihalides by using various reagents such as PX_5[153,154], $SOCl_2$[155,156], BBr_3[157], or $N_2H_4/CuX_2–Et_3N$[158]) (Scheme 19). The selective mixed-coupling of *gem*-dibromides with carbonyl compounds to furnish alkenes is successfully achieved using the $TiCl_4–Zn–TMEDA$ system (Eq. 36).[159]

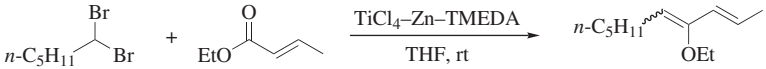


Scheme 19

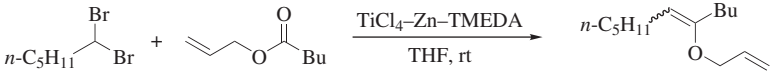


(Eq. 36)

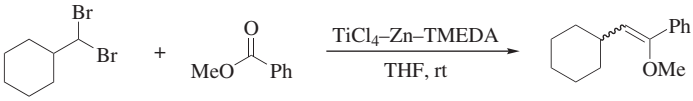
The advantage of this method is that it is applicable to the alkenylation of carboxylic acid derivatives such as esters, thioesters, and amides, as well as aldehydes and ketones (Eqs. 37–39,[160] 40,[161] and 41[162]). It is desirable to use pyrometallurgy-grade zinc that contains 0.04–0.07 mol % of lead based on zinc.[163]



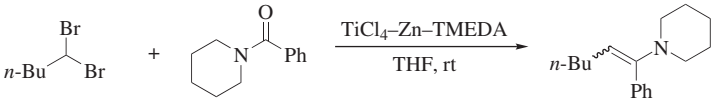
(90%) (*E*)/(*Z*) = 6:94 (Eq. 37)



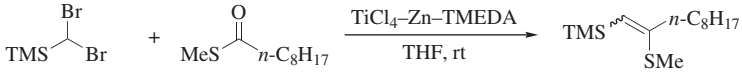
(52%) (*E*)/(*Z*) = 8:92 (Eq. 38)



(61%) (*E*)/(*Z*) = 10:90 (Eq. 39)

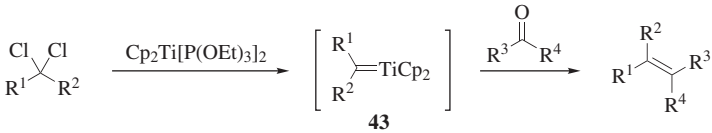


(80%) (*E*)/(*Z*) = 96:4 (Eq. 40)



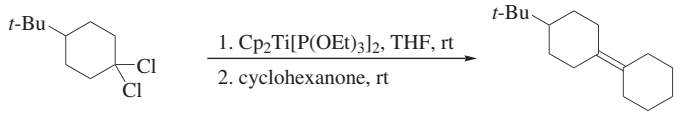
(80%) (*E*)/(*Z*) = 34:6 (Eq. 41)

An alternative method for the mixed-coupling of *gem*-dihalides with carbonyl compounds employs $Cp_2Ti[P(OEt)_3]_2$, which is prepared by the reduction of Cp_2TiCl_2 with magnesium in the presence of triethyl phosphite and 4 Å molecular sieves (Scheme 20). A variety of tetrasubstituted alkenes are obtained by the mixed-coupling between highly substituted *gem*-dichlorides and carbonyl compounds including aldehydes, ketones, esters, and lactones (Eqs. 42,[164] 43,[165] and 44[164]). The reaction is assumed to proceed via the formation of titanium carbene complexes **43**. Ketene equivalents, 1,1-dichloroalkenes, may be also employed in the mixed-coupling with aldehydes and ketones (Eqs. 45 and 46).[166]

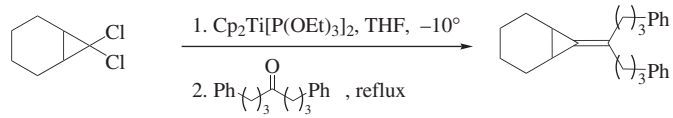


43

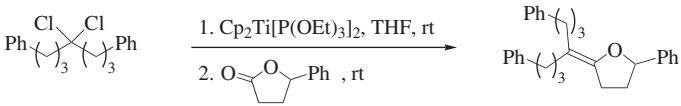
Scheme 20



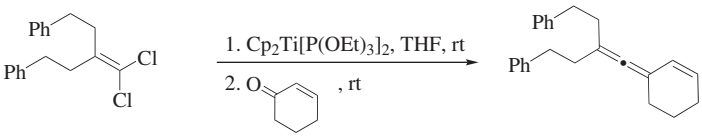
(73%) (Eq. 42)



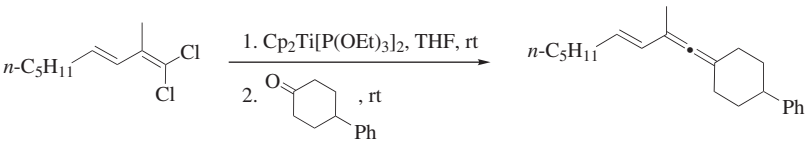
(64%) (Eq. 43)



(72%) (Eq. 44)



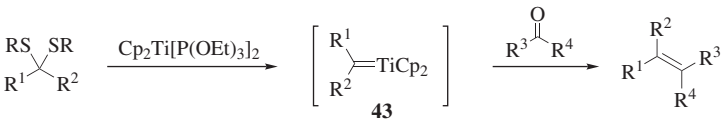
(70%) (Eq. 45)



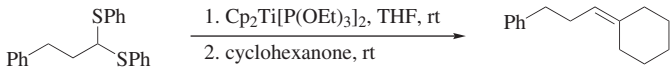
(60%)

(Eq. 46)

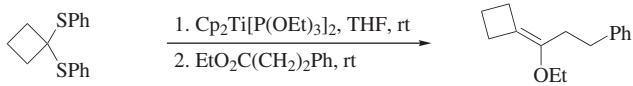
Carbonyl Olefination with Thioacetals. The titanocene(II)-promoted reaction of thioacetals with carbonyl compounds is also a good substitute for the McMurry coupling of two different carbonyl compounds. This reaction also proceeds by the formation of titanium carbene complexes **43** (Scheme 21).[167–169] Since thioacetals are readily prepared by the treatment of aldehydes and ketones with thiols in the presence of an appropriate acid catalyst and further derivatization of thioacetals, this method enjoys wide synthetic application (Eqs. 47,[170] 48,[171] 49,[170] 50,[172] and 51.[173] Although the mixed-coupling readily proceeds with diphenyl thioacetals of aldehydes, the reaction using thioketals produces alkenes only when thioketals of sterically less-congested ketones such as acetone and cyclobutanone are employed.



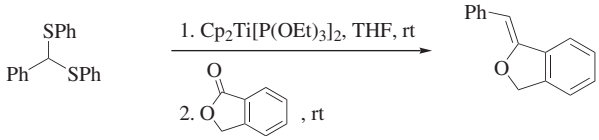
Scheme 21



(69%) (Eq. 47)

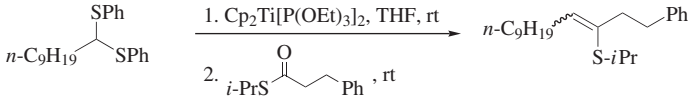


(80%) (Eq. 48)



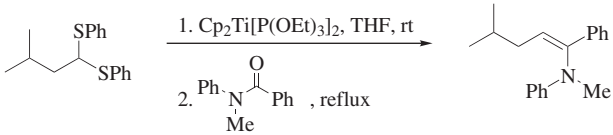
(75%) $(E)/(Z) < 1:99$ $E:Z$

(Eq. 49)



(84%) $(E)/(Z) = 19:81$

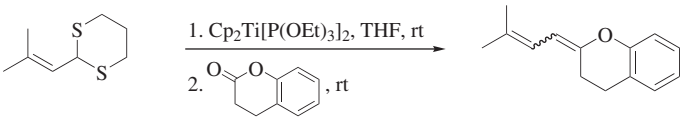
(Eq. 50)



(76%) $(E)/(Z) < 1:99$

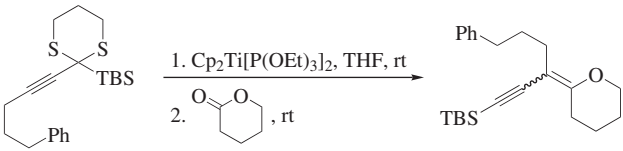
(Eq. 51)

The reaction of thioacetals of unsaturated aldehydes with carbonyl compounds provides a method for the preparation of 1,3-dienes (Eq. 52).[170] Thioacetals of alkynyl silyl ketones may also be subjected to coupling with carbonyl compounds (Eq. 53).[174,175] Reactions using dithio- and trithio orthoesters may be regarded as a mixed-coupling of formic acid esters with carbonyl compounds (Eqs. 54[176] and 55[177]).

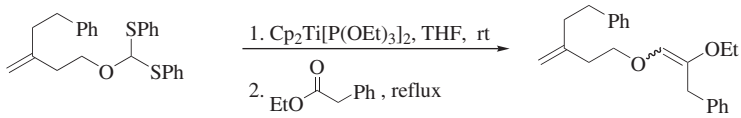


(64%) $(E)/(Z) = 38:62$

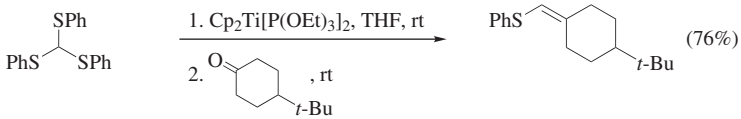
(Eq. 52)



(71%) single isomer (Eq. 53)

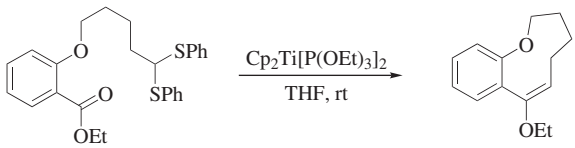


(80%) (*E*)/(*Z*) = 62:38 (Eq. 54)

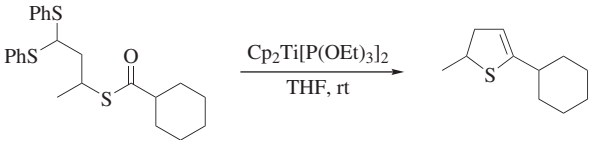


(76%) (Eq. 55)

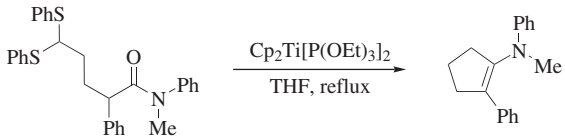
The titanocene(II)-promoted, intramolecular coupling between thioacetals and carboxylic acid derivatives furnishes unsaturated cyclic compounds. The reaction is applicable to the preparation of a variety of heterocyclic and heteroatom-substituted cyclic compounds with different ring sizes (Eqs. 56,[178] 57,[179] and 58[180]).



(70%) (Eq. 56)



(65%) (Eq. 57)



(89%) (Eq. 58)

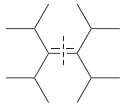
APPLICATIONS TO SYNTHESIS

Applications of the McMurry coupling include the preparation of sterically congested and strained alkenes that are otherwise difficult to prepare by conventional methods. Another synthetic use is for the preparation of theoretically interesting and structurally unique alkenes. These include polyenes, ethylene-bridged porphyrins, rigid stilbenes, and 1,2-(bis)metallocenylethenes. Intramolecular couplings of dicarbonyl compounds are used for the preparation of cyclophan-1-enes, dihydropyrroles and thiophenes, and condensed polyaromatics. Compounds bearing medium and large rings are also synthesized effectively by intramolecular coupling of dicarbonyl compounds. In this regard, construction of cyclic natural products with various ring sizes has been achieved. Tandem cyclizations have been employed to synthesize π-conjugate macrocycles such as ethylene-bridged cyclic bi- and ter-aryls and their heterocyclic analogues. Biologically

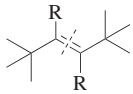
active triphenylethene derivatives such as tamoxifen (an antagonist of the estrogen receptor in breast tissue) and cyclooxygenase inhibitors are widely prepared by the mixed McMurry coupling.

Synthesis of Sterically Hindered and/or Strained Alkenes

In general, simple dialkyl ketones and cycloalkanones are converted into the corresponding alkenes in good to high yields by homocoupling with the low-valent titanium reagents. The homocoupling of sterically encumbered acyclic aliphatic ketones provides convenient access to strained tetrasubstituted alkenes, some of which are difficult to prepare by other methods. Thus, tetraisopropylethene (**44**) is obtained by the deoxygenative coupling of diisopropyl ketone using the $TiCl_3(DME)_{1.5}$–Zn/Cu system in 87% yield.[6] The homocoupling of *tert*-butyl methyl ketone[181] using the $TiCl_3$–Zn system and *tert*-butyl ethyl ketone[182] using the $TiCl_3$–$LiAlH_4$ system produces the corresponding alkene **45** with excellent (*E*)-selectivity. However, the preparation of the elusive tetra-*tert*-butylethene by the McMurry coupling has not yet been reported.

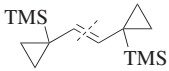


44 (87%)

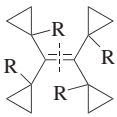


45
R = Me (65%), (*E*) only
R = Et (47%) (*E*)/(*Z*) = 12:1

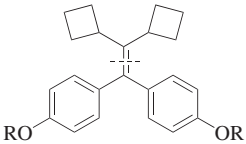
The McMurry coupling of aldehydes and ketones bearing strained small rings provides access to alkenes containing such rings. For example, the homocoupling of cyclopropyl aldehydes and ketones furnishes alkenes bearing cyclopropyl rings **46**[43] and **47**.[183,184] The dicyclobutyl ketone can be employed for the mixed-coupling the acetophenones to produce the dicyclobutylethenes **48**.[185]



46 (38%)

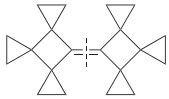


47
R = H (15%); R = Me (13%)

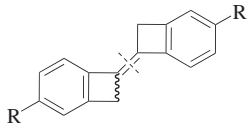


48
R = H (18%); R = Me (87%)

The McMurry coupling of strained cyclic ketones constitutes a convenient route to strained alkenes. The homocoupling of trispiro[2.0.2^4.0.2^7]decan-10-one furnishes the fully spirocyclopropanated bi(cyclobutylidene) **49**.[186] Similarly, benzocyclobutanones afford the bi(cyclobutylidenes) **50** as (*E*)/(*Z*) mixtures.[187,188] Cyclobutanone can also be applied to the mixed-coupling with 4,4′-methoxybenzophenone to give the corresponding alkene **51** in 87% yield.[189]

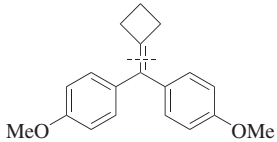


49 (28%)



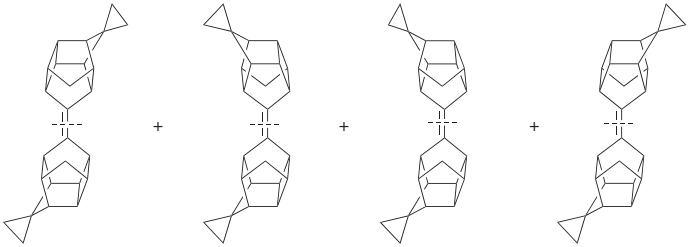
50

R = H (22%) (*E*)/(*Z*) = 1:1
R = Me (6%) (*E*)/(*Z*) = —



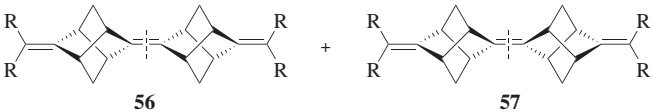
51 (87%)

The McMurry coupling is frequently employed for the preparation of sterically crowded alkenes having unique and/or unusual structures. The highly compact and often strained polycyclic cage hydrocarbons connected with carbon–carbon double bonds are prepared by the low-valent titanium-promoted deoxygenative coupling of polycyclic ketones.[190–193] These compounds are of interest as potential materials for high-energy/high-density fuels. Thus, the coupling of 4-(spirocyclopropyl)pentacyclo[5.4.0.0.^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one leads to an isomeric mixture of alkene dimers **52**–**55**.[191] The titanium-promoted deoxygenative coupling of 6-alkylidenetricyclo[3.3.0.0^{3,7}]octan-2-ones yields a mixture of the racemic (**56**) and meso isomers (**57**) of distella-2,2′,6,6′-trienes. These alkenes are considered as models for investigation of through-space interaction of isolated double bonds.[194,195] The highly twisted bis-exocyclic cisoid diene **58** is prepared by the coupling between acetone and (+)-pulegone.[196]



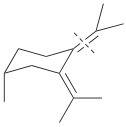
52 + **53** + **54** + **55**

52 + **53** + **54** + **55** (46%)



56 **57**

R = H, **56** + **57** (12%), **56**/**57** = 98:2
R = Me, **56** + **57** (1.3%), **56**/**57** = 98:2

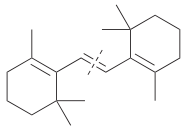


58 (50%)

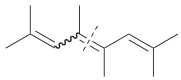
Synthesis of Highly Conjugated Molecules

The homocoupling of enals and enones is a useful method for the preparation of symmetrical acyclic polyenes. For example, aliphatic trienes **59**[110] and **60**[129] can be synthesized by the titanium-mediated coupling of the corresponding

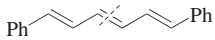
enal and enone respectively. Similarly, the trienes having phenyl ((*E*,*E*,*E*)-**61**)[121] and 1-azulenyl (**62**)[197] groups at either end are also obtained with the all (*E*)-configuration of the triene moiety. When the $NbCl_5$–Li system is used for the coupling of cinnamyl aldehyde, the triene **63** is formed with the (*E*,*Z*,*E*)-configuration.[96]



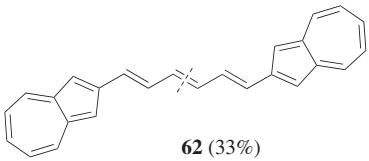
59 (94%)



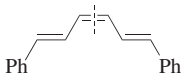
60 (*E*)-isomer (60%) + (*Z*)-isomer (25%)



61 (83%)

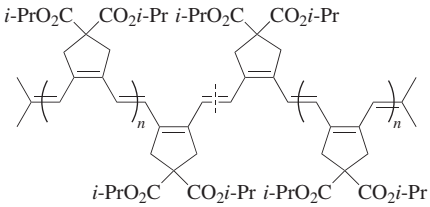


62 (33%)



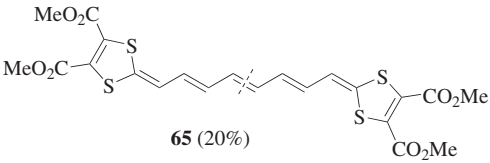
63 (55%)

The McMurry coupling can be applied to the preparation of a wide variety of symmetrical pentaenes and higher polyenes. The deoxygenative homocoupling of the corresponding dienal, tetraenal, and hexaenal yields the pentaene **64** ($n = 0$), nonaene **64** ($n = 1$), and tridecaene **64** ($n = 2$).[198] The polyenic analogue of tetrathiafulvalene **65**, in which two dithiole moieties are separated by a pentaene moiety, has also been synthesized.[199] Fully cross-conjugated pentaene **66** is obtained by the coupling of 4,4-dimethylcyclohexa-2,5-diene.[200]

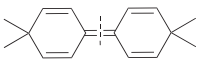


64

n	Yield (%)
0	61
1	82
2	25



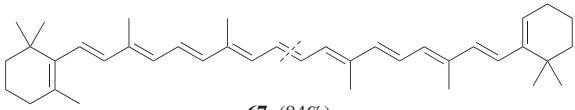
65 (20%)



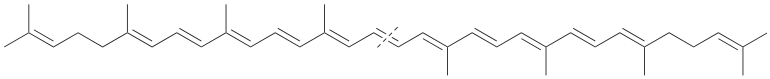
66 (97%)

β-Carotene (**67**) and lycopene (**68**) are synthesized by treatment of retinal and γ-retinal in 84 and 75% yields, respectively, with the $TiCl_3$–$LiAlH_4$ system.[201] Other titanium reagents such as $TiCl_4$–Zn,[202] titanium powder–TMSCl,[83] and

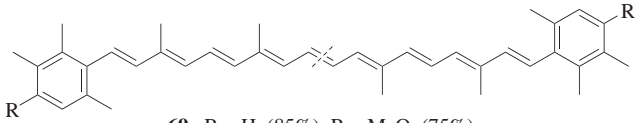
$TiCl_3-Li$[27] have been used for the β-carotene synthesis. Isorenieratenes (**69**) (carotenide light-harvesting pigments) are prepared in a similar manner.[203] The unsymmetrical heptaene **70** is synthesized as a stereoisomeric mixture by the mixed-coupling of the tetraenone and dienone using the $TiCl_4-Zn$ system.[204]



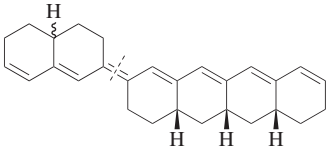
67 (84%)



68 (75%)



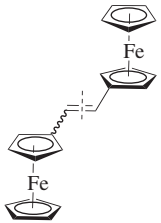
69 R = H (85%); R = MeO (75%)



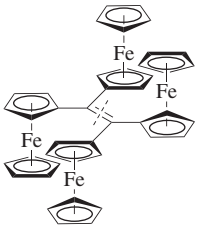
70 (40.8%)

Metallocenes and related structural units are tolerant to the McMurry coupling conditions. Thus, the homocoupling of metallocene-substituted aldehydes and ketones and related compounds provides access to symmetrical alkenes with metallocene units or η^5-cyclopentadienyl complexes. 1,2-Diferrocenylethene (**71**)[205] and tetraferrocenylethene (**72**)[206] can be prepared from ferrocenecarbaldehyde and diferrocenyl ketone, respectively, by low-valent titanium-promoted deoxygenation. The η^4-1,3-cyclobutadienyl-iron complex substituted ethene **73** is obtained with (*E*)-stereoselectivity by the $TiCl_3-LiAlH_4$ system-promoted homocoupling of the corresponding aldehyde.[207] The (*Z*)-alkenes **74** (R = Me) having a phosphacyclopentadienyl manganese unit are formed as *rac/meso* mixtures by the coupling of the corresponding methyl ketone (R = Me).[208] When the corresponding phenyl ketone is subjected to similar coupling conditions, the (*Z*)-isomer **74** (R = Ph) is selectively obtained. Cynchridene is transformed into (*E*)-1,2-bis[(η^5-cyclopentadienyl)dicarbonylnitrosylchromium]ethene (**75**) in a similar manner.[205]

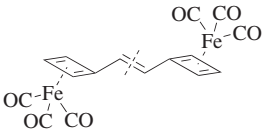
Alkenes bearing nitrogen-containing heteroaromatic units may be synthesized by McMurry methods. *N*-Alkoxycarbonylpyrrolecarbaldehyde undergoes deoxygenative coupling using the $TiCl_3-Li$ system to give the di(2-pyrrolyl)ethenes **76**,[124] whereas the coupling of the *N*-unsubstituted 2-pyrrolecarbaldehyde under



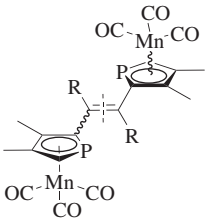
71 (25%) (*E*)/(*Z*) = 3.5:1



72 (75%)

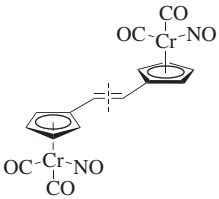


73 (56%)



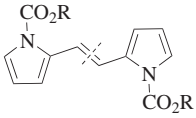
74

R = Me (*Z*)-*rac* (45%) + (*Z*)-*meso* (27%)
R = Ph (*E*)-*rac* (41%)



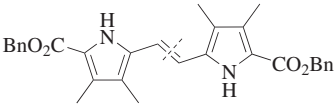
75 (36%)

similar conditions results in the formation of a complex mixture. Using 2-pyrrolecarbaldehydes bearing an ester group at the 5-position leads to di(*N*-unsubstituted pyrrolyl)ethenes **77**.[209,210] By contrast, the use of the corresponding 3-pyrrolecarbaldehydes lowers the yield of the alkenes.[211] Pyridine-substituted alkenes **78** and **79** are obtained by the homocoupling of 3-[212] or 4-pyridinecarbaldehyde, respectively.[124] Treatment of 4,5-diazafluorenone with the $TiCl_3$–$LiAlH_4$ system gives bis(4,5-diazafluorenylidene) (**80**), but a similar reaction of the 1,8-diaza-isomer fails to produce the corresponding alkene.[213]

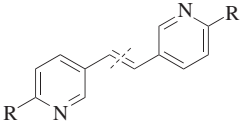


76

R = Me (50%); R = Et (30%)

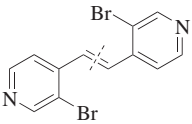


77 (81%)

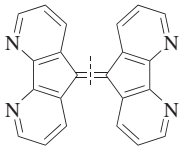


78

R = MeO (40%); R = MeS (30%)

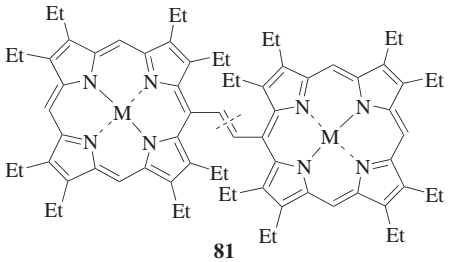


79 (30%)



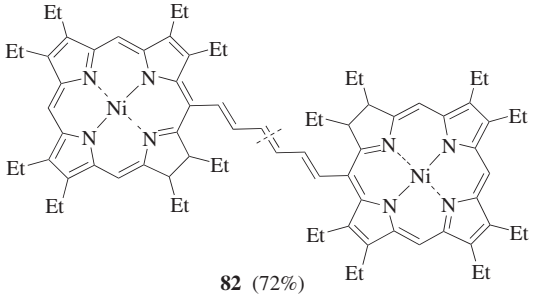
80 (20%)

Deoxygenative coupling can be applied to form porphyrin or chlorin dimers linked by conjugate systems. These compounds are of importance for understanding the processes of photosynthesis. Metalloporphyrin and chlorin substructures are compatible with the McMurry coupling conditions; thus, the ethene-bridged prophyrins **81**,[49,214] triene-bridged porphyrins **82**,[215] and their chlorin counterparts **83**[215] are obtained from the corresponding aldehydes. The reaction frequently provides (*E*)/(*Z*) mixtures with regard to the newly formed double bond and, in some cases, the (*Z*)-isomers predominate. This selectivity likely results from a strong π-π pre-association of the large conjugate system.

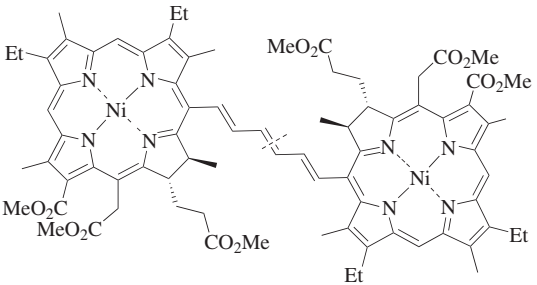


81

M	Yield (%)	(*E*)/(*Z*)
Ni	72	39:33
Cu	70	0:100

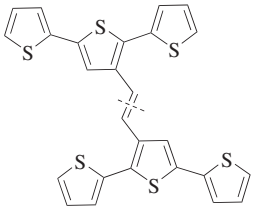


82 (72%)

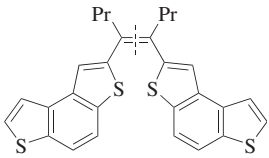


83 (84%)

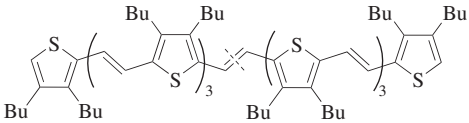
Aldehydes containing various thiophene substructures are amenable to the McMurry coupling. Such substructures include not only simple thiophenes but also oligothiophenes **84**,[216] condensed thiophenes **85**,[217] oligo(thienylenevinylene)s **86**,[218] or more complex structures.



84 (66%)



85 (*E*) isomer (7%)
+ (*Z*) isomer (93%)

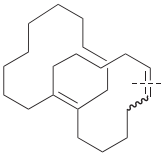


86 (52%)

Synthesis of Ring Compounds with Unique Structures

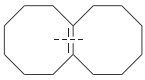
Cycloalkenes of ring sizes 3–16 and larger are prepared by the intramolecular McMurry coupling of dicarbonyl compounds. The yields of medium-sized and larger rings are remarkably high relative to other methods.[23] Construction of simple and saturated ring systems are described in the "Scope and Limitations" section. This section focuses on the preparation of rings with unique structures.

Bicyclic systems such as the chiral *trans*-fused (*R*)-(+)-[10.10]betweenanene **87**,[219] the bridgehead alkene **88**,[220] and bicyclo[6.6.0]tetradec-1(8)-ene (**89**)[221] have been prepared by the intramolecular McMurry coupling of the corresponding dicarbonyls. Compound **88**, which is difficult to prepare by other methods, has been converted to a cation in order to investigate a bent three-center, two-electron, C–H–C bond. The tricyclodecadiene **90** has also been synthesized for the study of the through-space interaction of two π systems, located perpendicular to each other.[222] These results demonstrate that this process is effective for the construction of medium rings with strained structures.

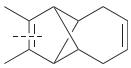


87 (44%)

88 (36%)

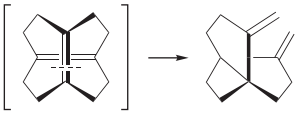


89 (72%)

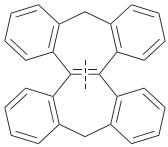


90 (13%)

The process has also been used to prepare the highly strained, unstable 7-membered cycloalkene **91**, which is transformed into the tricyclic diene **92** by a subsequent Cope rearrangement.[223] The transannular coupling also proceeds to give **93** if the two carbonyl groups are properly located.[224]



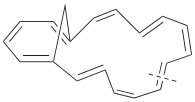
91 **92** (50%)



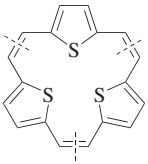
93 (81%)

Another application of the McMurry coupling is the construction of cyclic conjugated polyenes. A variety of polyenes such as [12]-, [14]-, [18]-, [20]-, and [24]annulenes are obtained by intramolecular coupling. The bridged [14]annulene **94**[225] with a phenanthrene perimeter and [18]annulene **95**[226] are of interest in the context of aromaticity. Tandem cyclization is used for the preparation of sulfur-bridged [18]annulene **96**.[149]

94 (35–40%)



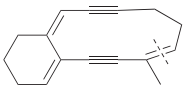
95 (12%)



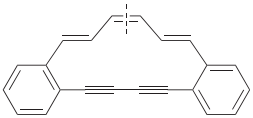
96 (38%)

Strained cyclic enynes are analogously prepared from the corresponding dicarbonyl compounds. Thus, cyclo-1,3-dien-5-ynes **97** with ring sizes of 10–14 are synthesized by the deoxygenative cyclization of α,ω-dialdehydes.[227] These are transformed into benzocycloalkanes by thermal isomerization. The bicyclotriendiyne **98** is prepared as a model of a chromophore of the anti-tumor antibiotic neocarzinostatin by the cyclization of the dienediyne keto aldehyde.[228] The cyclotrienediyne **99** and its higher vinylogues, the bisdehydrodibenzo[16]-, [18]-, [20]-, and [22]annulenes, are similarly prepared; their yields decrease from 27 to 4% with increasing ring size.[229]

97 (5–44%) $n = 4–8$



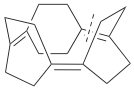
98 (47%)



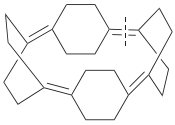
99 (27%)

Other ring compounds with novel structures include triene **100**[230] and tetraene **101**,[231] in which six-membered rings are connected with C–C double bonds at the C1 and C4 positions. These compounds are prepared from the corresponding diketones. Compound **101** acts as an eight-electron square-planar ligand to form a complex with Ag(I). $[6.8]_3$Cyclacene **102** is a hoop-shaped molecule consisting

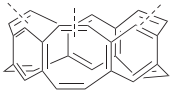
of annulated unsaturated rings and is synthesized by the 3-fold intramolecular ring closure of the hexaaldehyde.[232]



100 (24%)



101 (90%)

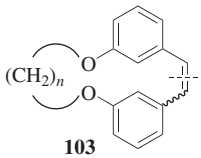


102 (8%)

Synthesis of Cyclophanes, Helicenes, and Related Compounds

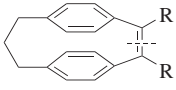
The low-valent titanium-promoted intramolecular cyclization of tethered bis(aromatic carbonyl compounds) is employed for the preparation of [2.*n*]cyclophan-1-enes in which each aromatic ring is connected to the other by an ethylene bridge. A variety of *o*-, *m*-, and *p*-cyclophan-1-enes are prepared from bis(arenecarbaldehydes) and bis(aryl ketones) having various aliphatic chain tethers such as oligo(methylene) and oligo(ethylene oxide). The geometry of the double bond formed is dependent on the length of the tethers. For example, the (*Z*)-isomer of metacyclophane **103** ($n = 3$) with a trimethylene chain predominates, whereas the (*E*)-isomer **103** ($n = 6$) with a hexamethylene chain is formed preferentially.[233] The highly strained paracyclophan-1-enes **104** can be synthesized by the intramolecular cyclization of trimethylene-tethered alkanophenones in good yields by slow addition of the diketones to a large excess of the titanium reagent.[234] The McMurry coupling of 4,13-dibenzoyl[2.2]paracyclophane provides 4,13-(α,α′-stilbeno)[2.2]paracyclophane (**105**), a triply bridged cyclophane, in good yield.[235]

Preparation of [2.*n*]cyclophan-1-enes with tethers containing aromatic rings is achieved by the intramolecular McMurry coupling of dicarbonyl compounds. Thus, the stilbenoprismand **106**, a new class of polyaromatic receptors with a Δ-shaped cavity, is prepared by the coupling of the corresponding diketone.[236] Bis(benzaldehydes) linked with an enantiomerically pure (*S*)-1,1′-bi-2-naphthol unit at the *ortho, meta*, and *para* positions are converted to the chiral receptors [2,n]cyclophan-1-ene **107** when subjected to the McMurry coupling.[237]



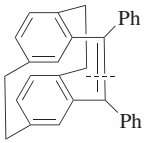
103

n	Yield (%)	(*E*)/(*Z*)
3	65	0:100
6	95	90:10

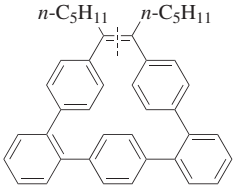


104

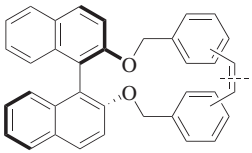
R	Yield (%)
Me	82
Et	60



105 (79%)



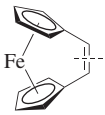
106 (93%)



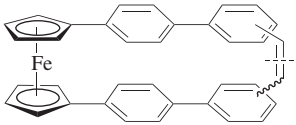
107

	Yield (%)
ortho	52
meta	62
para	15

The vinylene-bridged *ansa*-ferrocene **108** is prepared by slow addition of 1,1′-ferrocenedicarbaldehyde to the $TiCl_3$–Zn/Cu system.[238] The intramolecular reductive coupling of *o*-, *m*-, and *p*-benzaldehydes connected by a ferrocene-containing linker leads to the biphenylenevinylene-bridged ferrocenophanes **109**.[239] The (*E*)/(*Z*) ratios of the double bonds formed are dependent on the position of the formyl group.



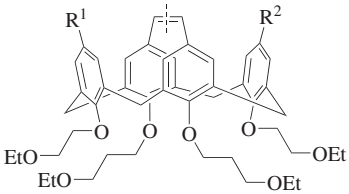
108 (44%)



109

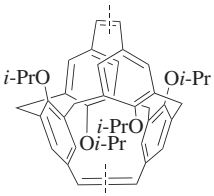
	Yield (%)	(*E*)/(*Z*)
ortho	59	34:35
meta	28	100:0
para	32	0:100

The intramolecular reductive coupling of bis(arenecarbaldeydes) described above can be applied to calix[4]arenes bearing formyl groups at the appropriate positions to produce intramolecularly double-bond-bridged calix[4]arenes. Thus, the ethylene-bridged calix[4]arenes **110** are obtained with (*E*)-stereoselectivity from the calix[4]arenes bearing two formyl substituents on the opposite benzene rings.[240] When the 1,3-alternate *p*-formylcalix[4]arene is employed, two-fold cyclization takes place between two formyl groups at the opposite side of the molecule to give the caged calix[4]arene **111**.[241] The reaction of calix[4]arenes having two benzaldehyde moieties connected by an ethylene oxide linker yields the stilbene-bridged calix[4]arenes **112**;[242] the configuration of the alkene is dependent on the substitution pattern of formyl groups.

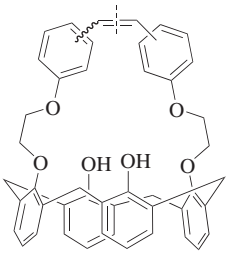


110

R^1, R^2 = H, Me, *t*-Bu (15–30%)



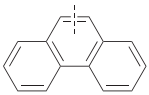
111 (25%)



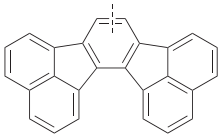
112

	Yield (%)	
	(*E*)-**112**	(*Z*)-**112**
ortho	15	62
meta	37	37
para	—	87

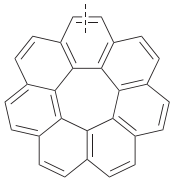
The intramolecular cyclization of 2,2′-diformylbiaryl derivatives and related compounds is employed for the preparation of various condensed polycyclic aromatic compounds. Phenanthrene (**113**)[243] and acenaphtho[1,2-j]fluoranthene (**114**)[243] are representative examples. The analogous compound, [7]circulene (**115**), in which seven benzene rings are circularly arranged in a strained saddle shape, is synthesized in a similar manner.[244] The aromatic ring construction by the intramolecular McMurry coupling has been also applied to the preparation of helicenes. Thus, the enantiomerically enriched [7]thiahelicenes **116**[245] are synthesized from the corresponding enantiomerically pure biaryl dialdehydes in good yields. This method is a good alternative to the oxidative photocyclization of a stilbene-type precursor. Similarly, the thiophene-based [7]helicene **117** is obtained from an axially chiral biaryl diketone.[246] In both cases, a stereochemical correlation between the (*R*) axial chirality of the biaryl dicarbonyl compounds and the (*M*) helical chirality of the helicenes is observed.



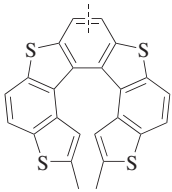
113 (67%)



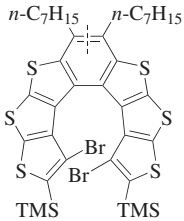
114 (56%)



115 (35%)



(*M*)-(–)-**116** (53%), er >99.5:0.5
(*P*)-(+)-**116** (52%), er >99.5:0.5



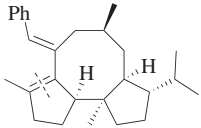
(*M*)-(–)-**117** (28%), er 87.0:13.0
(*P*)-(+)-**117** (17–63%), er 75:25 to 95:5

Total Synthesis of Natural Products

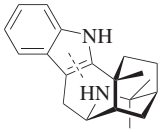
Many synthetic applications of the McMurry coupling in total syntheses of natural and related products have appeared as the process is efficient in constructing various macrocycles. Furthermore, the reaction can be carried out successfully in the presence of a variety of functional groups by the judicious choice of the reagents and reaction conditions.

The low-valent titanium-promoted intramolecular cyclization has been applied to the total synthesis of five-membered-ring natural products such as (±)-strigol[247], (±)-hirsutene[248], (±)-7,8-epoxy-4-basmen-6-one (**118**)[249] and (±)-araneosene.[250] (+)-Aristoteline (**119**), a naturally occurring indole alkaloid, can also be synthesized using this system.[7] Bicyclic six-membered-ring formation by the

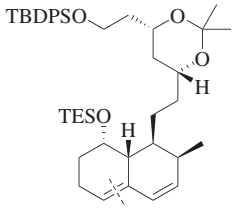
intramolecular coupling of dicarbonyl compounds is employed for the total synthesis of (+)-compactin (**120**)[251], (+)-mevinolin[251], and (+)-ipalbidine,[252] and the tricyclic ring formation leads to a hybrid analog of huperzine A and B.[253] A six-membered ring in spirocyclic (±)-α-chamigrene,[254] tricyclic (±)-isokhusimone (**121**),[255,256] and the steroid skeleton of 9(11)-dihydroestrone methyl ether (**122**)[257,258] are constructed by a similar cyclization. Seven-membered-ring formation is employed in the synthesis of bicyclic (±)-clavukerin A and isoclavukerin A.[259] The tetracyclic diterpene kempene-2 (**123**) is synthesized by the cyclization of a dialdehyde to form a seven-membered ring at the final stage.[260] A tricyclic system involving an eight-membered ring is constructed in the syntheses of the ABC system of taxol,[261] taxane triene **124**, which comprises the full and stereochemically correct carbon framework of natural taxusin,[262] and the ceroplastin nucleus.[263,264] The ten-membered-ring sesquiterpenes, bicyclogermacrene (**125**)[265] and its stereoisomer, lepidozene,[265,266] dihydrogermacrene,[267] and helminthogermacrene[268] are prepared through the low-valent titanium-promoted cyclization. Eleven-membered ring formation by the intramolecular coupling of keto aldehydes is involved in the syntheses of the tricyclic trinervitane skeleton **126**[269] and humulene (**127**).[270] Twelve-membered-ring formation is applied to the total synthesis of verticillene (**128**), a biogenetic precursor of taxane alkaloids.[271,272] The intramolecular cyclization of keto aldehydes for 14-membered-ring formation is used often in the synthesis of many cembrenoide diterpenes such as (±)-cembrene-A,[273] cembrene-C (**129**),[274–276] (+)-3,4-epoxycembrene-A,[277,278] (+)-11,12-epoxycembrene-C[279] and its 11,12-dehydro derivative,[280] (−)-[281] and (±)-[282] 13-hydroxyneocembrene (**130**), (−)-13-hydroxy-11,12-epoxy-neocembrene (**131**),[283] (±)-sarcophytols A and B,[284] (±)-sarcophytol A benzyl ether,[285] (±)-isosarcophytols A,[280] and (±)-crassin acetate methyl ether.[286] Synthesis of the marine cembranoid, (−)-1,3,11-cemratrien-6-ones,[287] preverecynarmin,[288] 14-deoxycrassin,[289] pseudoplexaural (**132**),[289] lepidozene,[267] and bicyclogermacrene[267] have been achieved via 14-membered-ring construction by the McMurry coupling. Syntheses of diterpene flexibilene (**133**),[290] sesterterpene terpestacin,[291] and its ring system[292] involve the formation of 15-membered rings. The macrocyclization of ansa-bridged benzofuranquinone (**134**) with an 18-membered ring is performed in the total synthesis of (±)-tridentoquinone.[293]



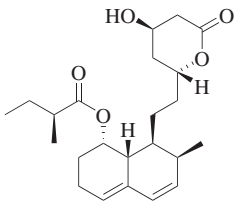
(±)-7,8-epoxy-4-basmen-6-one (**118**)
(73%)



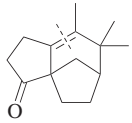
(+)-aristoteline (**119**)
(75%)



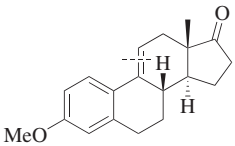
(85%)



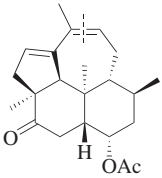
(+)-compactin (**120**)



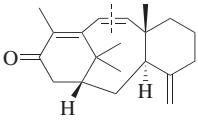
(±)-isokhusimone (**121**)
(57%)



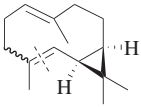
(+)-9(11)-dihydroestrone methyl ether (**122**)
(56%)



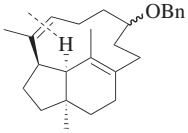
kempene-2 (**123**)
(32%)



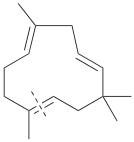
taxane triene (**124**)
(20%)



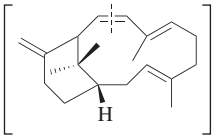
bicyclogermacrene (**125**)
(61%) (*E*)/(*Z*) = 80:20

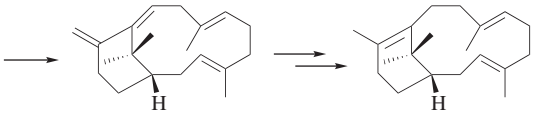


tricyclic trinervitane skeleton (**126**)
(11%)



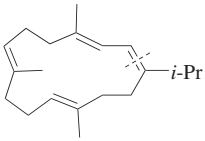
humulene (**127**)
(60%)



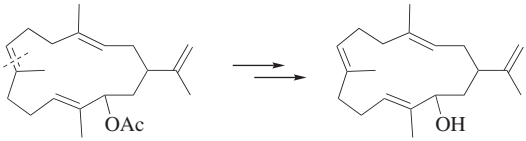


(23.5%)

verticillene (**128**)

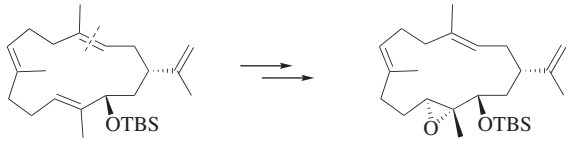


cembrene-C (**129**)
(72%)

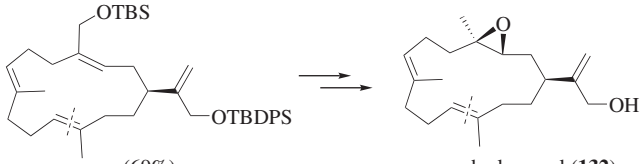


(38%)

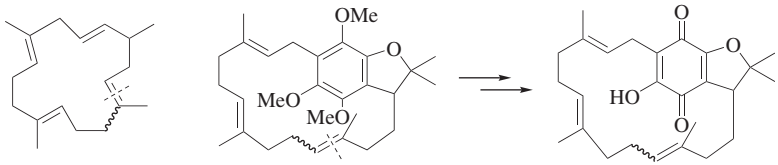
(±)-13-hydroxyneocembrene (**130**)



(81%) (–)-13-hydroxy-11,12-epoxy-neocembrene (**131**)



(69%) pseudoplexaural (**132**)



flexibilene (**133**) (79%) (*E*)/(*Z*) = 2:1 **134** (11%) (±)-tridentoquinone

COMPARISON WITH OTHER METHODS

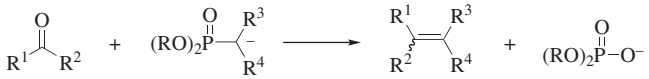
The McMurry coupling suffers some drawbacks compared to other direct carbonyl olefination reactions described below. For example, it generally affords statistical mixtures of homo- and mixed-coupling products in the intermolecular coupling of two different carbonyl compounds and tends to result in the formation of stereoisomeric mixtures of alkenes. Although some of the following direct deoxygenative olefination procedures should be considered in such cases, the simplicity of the experimental procedure, without pre-formation of any organometallic reagents, is an attractive feature of the McMurry coupling.

Wittig and Related Reactions

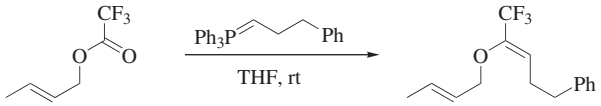
The Wittig reaction is perhaps the most widely used method for the direct transformation of carbonyl compounds to alkenes (Scheme 22).[294] One of its advantages is that the configuration of the olefination products can be controlled by careful selection of the phosphorus reagent and reaction conditions, especially in the case of the preparation of 1,2-disubstituted ethenes. The Horner–Wadsworth–Emmons reaction using α-carbanions of phosphonates (Scheme 23)[295] and the Horner–Wittig reaction using phosphine oxide anions are also powerful methods for carbonyl olefination. These reactions using phosphorous-based reagents, however, still suffer several disadvantages. First, unlike the McMurry coupling, they are seriously affected by steric hindrance and the preparation of tetrasubstituted alkenes using phosphorus-based reagents is virtually impossible. Second, the Wittig-type reactions are generally not effective for the olefination of carboxylic acid derivatives.

However, these so-called "non-classical Wittig reactions"[296] include the intermolecular olefination of electron-deficient esters and intramolecular olefination leading to the formation of certain cyclic compounds. Some examples are shown in Eqs. 59[297] and 60.[298]

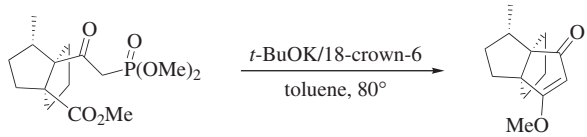
Scheme 22



Scheme 23



(65%) (Eq. 59)



(30%) (Eq. 60)

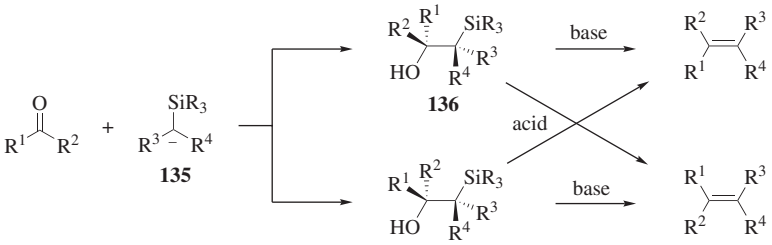
Peterson Olefination

The Peterson olefination consists of the addition of α-silyl carbanions **135** to carbonyl compounds and the subsequent elimination of silyloxide anions from the resulting β-hydroxyalkylsilanes **136** (Scheme 24).[299,300] The silanes **136** are usually isolated as mixtures of the two possible diastereomers by the protonation of the addition products when carbanions without an anion-stabilizing group are employed. The most striking feature of the Peterson olefination is that the two diastereomeric adducts **136** can be separated and the desired stereoisomers of alkenes can be obtained from either of the diastereomers depending on the reaction conditions employed for the elimination. Despite several characteristic features of the Peterson olefination, there remain some difficulties in terms of availability of adequate α-silyl carbanions and sensitivity to steric constraints.

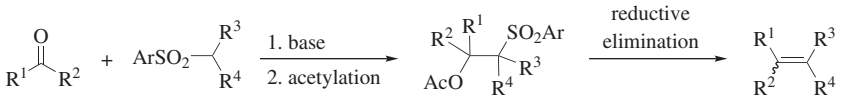
Julia–Lythgoe and Julia–Kocienski Reactions[301–305]

The Julia reaction (also known as the Julia–Lythgoe reaction) involves two separate steps: an addition of the α-carbanion of an aryl sulfone to a carbonyl compound and the reductive elimination of the resulting β-hydroxy sulfone (Scheme 25).[304]

The so-called modified Julia reaction (also known as the Julia–Kocienski reaction) is, in contrast, carried out in one pot and employed for the construction of a range of biologically active natural products as a tool for direct olefination

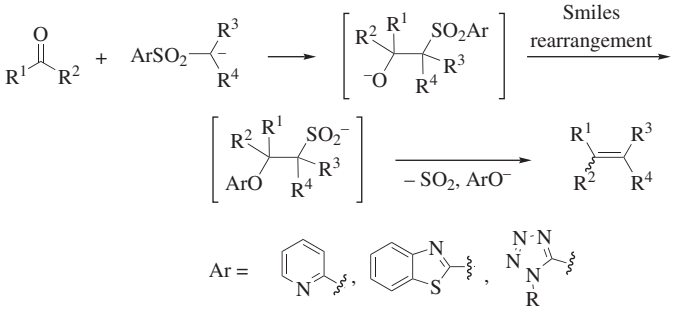


Scheme 24



Scheme 25

of aldehydes. The reaction consists of the addition of the α-anion of a heterocyclic sulfone to an aldehyde followed by Smiles rearrangement of the resulting β-alkoxysulfone and subsequent degradation of the sulfinate salt (Scheme 26).[304] The stereochemical course of the transformation is dependent on the nature of the heterocyclic moiety of the sulfone, the counter cation, and the reaction conditions. Generally (*E*)-alkenes predominate and high stereoselectivity is observed in certain cases. Excellent functional group compatibility is the synthetic advantage of the modified Julia reaction. Its major disadvantage over the McMurry coupling is its inapplicability to the preparation of highly sterically congested olefins.



Scheme 26

Carbonyl Olefination with Metal Carbene Complexes and Related Reactions

High-valent early transition-metal carbene complexes **137** possess ylide-like reactivity towards carbonyl compounds (Scheme 27).[167] Schrock first reported

that niobium and tantalum carbene complexes react with carbonyl compounds, including carboxylic acid derivatives, to produce the corresponding alkenes.[306] Shortly thereafter, synthetically useful Tebbe and related titanium-based reagents were developed for the generation of methylidenetitanocenes, which olefinate a variety of carbonyl compounds to give terminal olefins.[307] Although the olefination reactions of aldehydes, ketones, and carboxylic acid derivatives have been developed using alkylidenetitanocenes prepared from dialkyltitanocene,[308,309] inaccessibility of the carbene complexes bearing a β-hydrogen has limited their use. Development of the preparation of a range of titanium carbene complexes by the reductive titanation of thioacetals and related compounds with the titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$, however, has enabled the wide use of titanium carbene complexes for carbonyl olefination (see "Scope and Limitations" section).

Scheme 27

Several dimetallic reagents are employed for the deoxygenative transformation of carbonyl compounds to alkenes. The *gem*-dizinc reagent, generated by the $PbCl_2$-catalyzed reduction of CH_2I_2 with Zn or the CH_2X_2–Zn–$TiCl_4$ system transforms aldehydes, ketones, and esters into olefins in the presence of appropriate additives.[159] The organometallic reagents generated from the $RCHBr_2$–Zn–$TiCl_4$–TMEDA system are employed for the olefination of various carboxylic acid derivatives (see "Scope and Limitations" section). A synthetic advantage of these reactions is their applicability to the olefination of carboxylic acid derivatives.

The organochromium reagents generated by the reaction of $RCHBr_2$ with $CrCl_2$ transforms aldehydes to (*E*)-1,2-disubstituted ethenes with high stereoselectivity.[310] A marked advantage of this carbonyl olefination over the McMurry coupling is that the chromium reagents show high chemoselectivity toward aldehydes, and can be carried out in the presence of keto and ester functionalities.

EXPERIMENTAL CONDITIONS

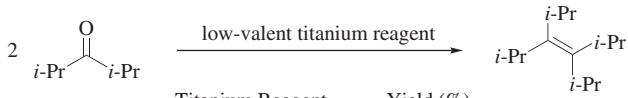
Preparation of Coupling Reagents: Stepwise vs One-pot Procedures

Since the first discovery of the deoxygenative coupling of carbonyl compounds, two types of procedures have been employed. A general procedure involving a stepwise sequence (formation of the reagent and then McMurry coupling) has been used in the coupling reaction using a variety of low-valent titanium species.[4,23] When highly reactive reducing agents, such as alkali metals or metal hydrides, are used for the generation of the low-valent titanium reagents, the stepwise procedure must be adopted. When the functional groups

present on the carbonyl compound are compatible with zinc as the reducing agent, a one-pot reaction involving the simple mixing of the titanium source, zinc, and the carbonyl compound can be performed.[3] This procedure can be used for the intramolecular coupling of oxo amides leading to the formation of indoles (so called "instant method").[7] The intramolecular McMurry coupling generally requires high-dilution conditions and slow addition of the substrate to avoid oligomerization. By contrast, the formation of heterocycles by the "instant method" does not require such special care. This protocol is also effectively employed for the intermolecular coupling of aldehydes.[241]

General Comments for the Preferred Conditions

Coupling Reagent. A variety of reagents have been developed for the McMurry coupling as described in the "Scope and Limitations" section. The choice of an appropriate reagent is crucial to obtain good yields of the desired products because different low-valent titanium species are formed depending on the particular titanium source, reducing agent, and conditions for its preparation. The $TiCl_3(DME)_{1.5}$–Zn/Cu system in DME seems to be the most versatile and reproducible reagent for both the inter- and intramolecular McMurry coupling (Scheme 28).[6,27] The $TiCl_4$–Zn–Py system and $TiCl_3$–C_8K system are also efficient for the coupling of a range of aldehydes and ketones.



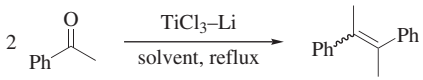
Titanium Reagent	Yield (%)
$TiCl_3$–$LiAlH_4$	12
$TiCl_3$–Zn/Cu	37
$TiCl_3$–K	37
$TiCL_3(DME)_{1.5}$–Zn/Cu	87

Scheme 28

Other reagents may be preferable depending on the carbonyl substrates. For example, the $TiCl_3$–$LiAlH_4$ system is employed for the oxo ester coupling, and the $TiCl_3$–Zn system is employed for the coupling of oxo amides through the "instant method."

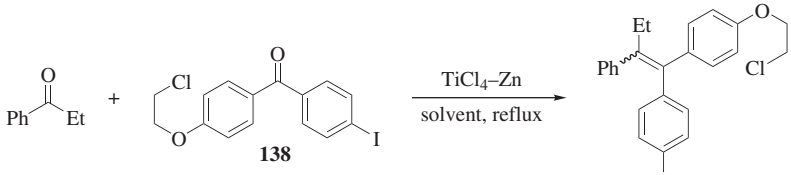
Solvent. Although the solvent-free McMurry coupling of benzophenone derivatives using the $TiCl_4$–Zn system has been reported,[311] the coupling is generally performed in ethereal solvents such as THF, DME, or 1,4-dioxane. The choice of a solvent is important to obtain good yields and selectivities. In several cases, THF and DME show different solvent effects. In the homocoupling of acetophenone with the $TiCl_3$–Li system, the reaction performed in DME preferentially furnishes the (*E*)-alkene whereas the (*Z*)-alkene predominates when THF is used (Scheme 29).[312] For the mixed-coupling of propiophenone

with benzophenone **138**, 1,4-dioxane is the solvent of choice to obtain the (*E*)-isomer in good yield (Scheme 30).[51] When 1,4-dioxane is replaced by THF, the (*Z*)-isomer slightly predominates.



Solvent	Yield (%)	(*E*)/(*Z*)
DME	92	83:9
THF	89	25:64

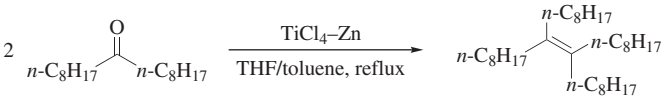
Scheme 29



Solvent	Yield (%)	(*E*)/(*Z*)
DME	35	1.3:1
THF	—	1:1.19
1,4-dioxane	56.5	3.9:1

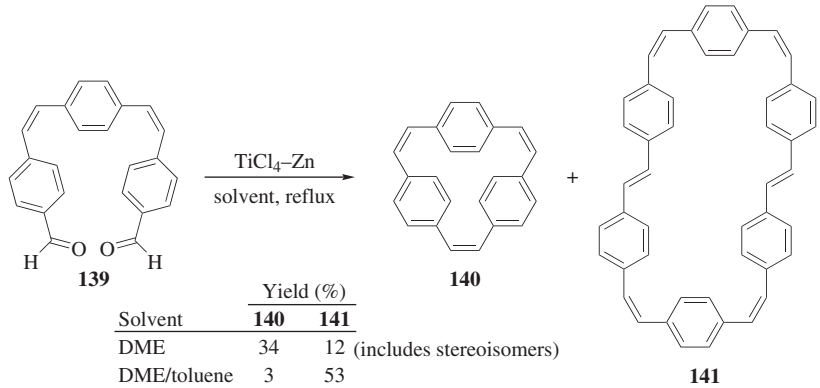
Scheme 30

Several reports describe the use of toluene as a co-solvent in the McMurry coupling. Although the preparation of 9,10-dioctyl-9-octadecene from dioctyl ketone could be achieved with difficulty and in low yields by the common variants of the McMurry coupling, the use of THF/toluene mixtures in the $TiCl_4$–Zn-promoted coupling affords the alkene in good yield (Eq. 61).[313] The combined use of toluene also affects the mode of intramolecular coupling. The deoxygenative cyclization of the dialdehyde **139** with the $TiCl_4$–Zn/Cu system carried out in DME produces the monomer **140** as a major product along with the dimer **141** as a mixture of stereoisomers (Scheme 31).[314] The dimer **141**, by contrast, is formed as a pure (*Z*,*Z*,*E*)-isomer by the reaction in a 1:1 mixture of DME and toluene.



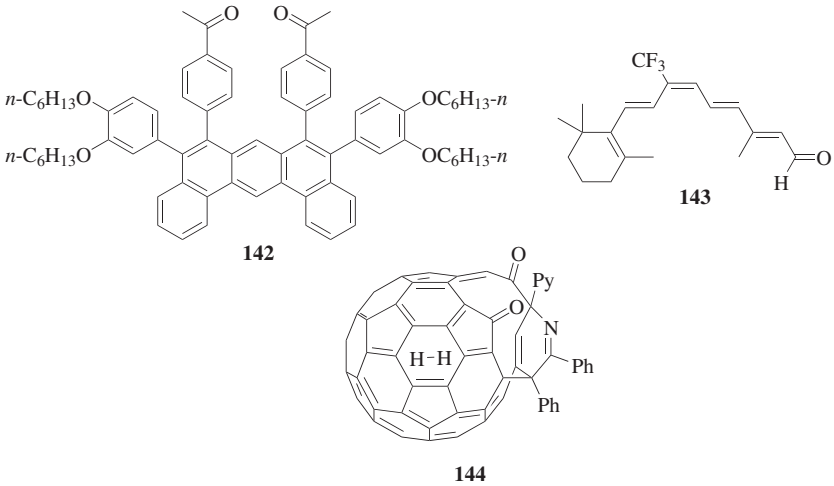
(70%) (Eq. 61)

Depending on the solubility of the substrates, the McMurry coupling may be carried out in mixed solvents. For example, THF/CH_2Cl_2 mixtures are employed for the $TiCl_4$–Zn promoted reaction of polyaromatic diketone **142**[315] and trifluoromethyl-substituted conjugated polyenal **143**.[122] THF/*o*-dichlorobenzene mixtures are employed for the intramolecular coupling of the fullerene derivative **144** encapsulating molecular hydrogen.[316]



Solvent	Yield (%) 140	141
DME	34	12 (includes stereoisomers)
DME/toluene	3	53

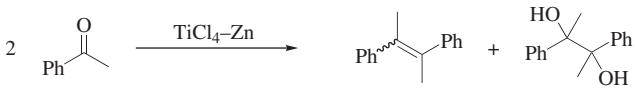
Scheme 31



In the intramolecular coupling of oxo amides leading to indoles by the "instant method" using the $TiCl_3$–Zn system, EtOAc, MeCN, and DMF are successfully employed in addition to ethereal solvents.[7]

Temperature. Most of the McMurry coupling reactions are carried out at elevated temperatures, conveniently at reflux of the solvent. Since the McMurry coupling generally proceeds via the initial formation of titanium pinacolates followed by the reductive elimination to form alkenes, pinacols are typical by-products of the McMurry coupling reactions. Pinacols may be the major products when the reactions are performed at lower temperatures; the $TiCl_4$–Zn-promoted reaction of acetophenone carried out in dioxane at reflux affords dimethyldiphenylethylene (**21**) exclusively but pinacol **22** is exclusively obtained when the

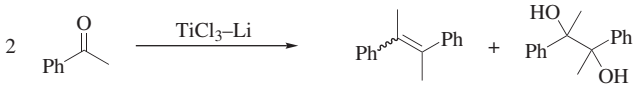
reaction is run at ambient temperature in THF (Scheme 32).[3] A similar tendency is observed in the $TiCl_3$–Li-promoted reaction of acetophenone (Scheme 33).[312]



		Yield (%)		
Solvent	Temp	**21**	**22**	
dioxane	reflux	92	0	
THF	rt	1	91	

21 **22**

Scheme 32



		Yield (%)		
Solvent	Temp (°)	**21**	**22**	
THF	reflux	89	0	
THF	30	52	25	
DME	30	0	38	
THF[a]	30	87	0	
DME[a]	30	0	75	

21 **22**

[a] The reaction was carried out under ultrasonication.

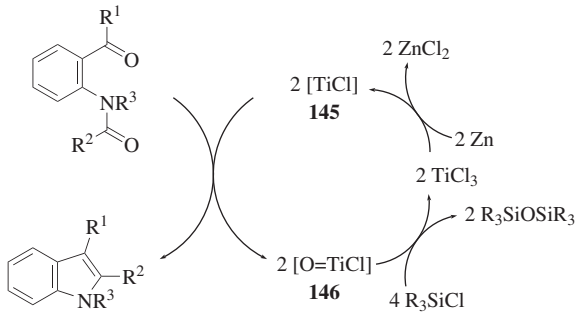
Scheme 33

Ultrasonication accelerates both the reduction of the titanium salts and formation of the alkenes in the above McMurry coupling; the reaction carried out in THF under irradiation of ultrasound proceeds at 30° and gives the same result as that carried out at reflux. Interestingly, however, the same reaction in DME results in the exclusive formation of the pinacol. The successful deoxygenative coupling of diferrocenyl ketone is achieved only under ultrasonication.[206] The McMurry coupling under microwave irradiation enjoys an advantage in that it is complete within a short period of time.[121,317]

High-Dilution Methods for Intramolecular Coupling. The intramolecular coupling of dicarbonyl compounds generally requires high-dilution conditions to obtain cyclic alkenes in good yields. Under the conditions suitable for intermolecular reactions, cycloalkenes are produced in rather low yield.[27] Therefore, the intramolecular coupling is typically performed by slow addition of the dicarbonyl compounds over several to dozens of hours by a motor-driven syringe pump to the refluxing solution of the coupling reagent. One of the exceptions is the intramolecular coupling of oxo amides leading to the formation of indoles. High dilution is neither necessary nor advantageous though the related formation

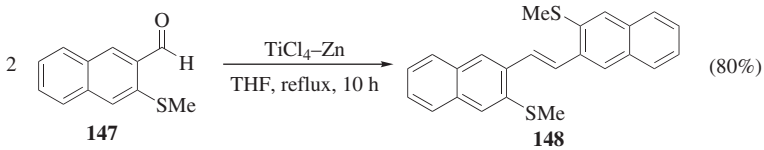
of benzofurans using the $TiCl_3-C_8K$ system requires high-dilution conditions.[79] The low-valent titanium reagent generated by the reduction of $TiCl_3$ with "high-surface sodium" (Na/Al_2O_3) is also recommended for the intramolecular coupling of dicarbonyl compounds to cycloalkenes since the reaction proceeds without using high-dilution techniques due to its pronounced template effect.[69] Because the second step of the tandem McMurry coupling of dicarbonyl compounds is an intramolecular cyclization, the high-dilution conditions are also employed in these reactions.

Catalytic McMurry Coupling. The preparation of indoles by the McMurry coupling with a catalytic amount of $TiCl_3$ has been realized by using trialkylchlorosilanes (Scheme 34).[83] In the catalytic cycle, the Ti(III) oxide **146** formed by the McMurry coupling of the oxo amides reacts with trialkylchlorosilanes to regenerate $TiCl_3$, which is then reduced with Zn to the low-valent titanium species **145** for further deoxygenative coupling. The procedure for the catalytic reaction is straightforward; heating a mixture of an oxo amide, $TiCl_3$, Zn dust, and a trialkylchlorosilane in MeCN furnishes the indole.



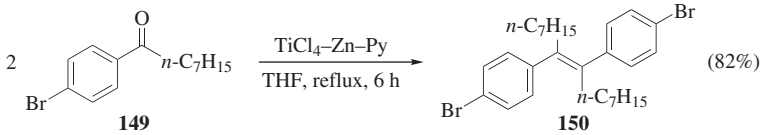
Scheme 34

EXPERIMENTAL PROCEDURES

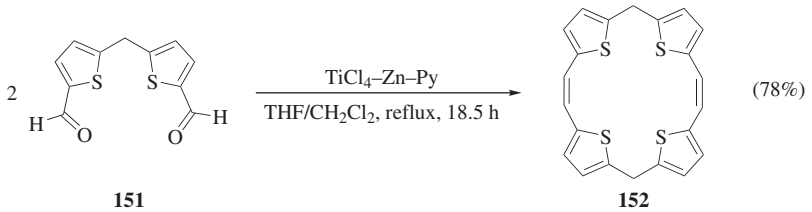


***trans*-1,2-bis(3-Methylthio-2-naphthyl)ethene (148) [Homocoupling with the $TiCl_4-Zn$ System].**[318] $TiCl_4$ (0.66 mL, 6.0 mmol) was slowly added to an

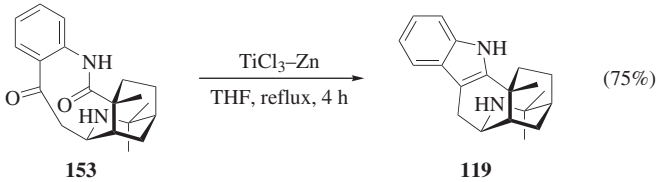
ice-cooled suspension of zinc powder (0.39 g, 6.0 mmol) in THF (10 mL), and the resulting mixture was heated to reflux for 1.5 h. After cooling to rt, a THF (10 mL) solution of **147** (0.405 g, 2.0 mmol) was slowly added and the mixture was heated to reflux for 10 h. After cooling to rt, the mixture was diluted with saturated aq. $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL) and further stirred for 3.5 h. The mixture was filtered through a Celite pad, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give **148** as yellow crystals (0.299 g, 80%). An analytical sample was obtained by recrystallization (CH_2Cl_2): mp 195.0–196.0°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 6H, S*Me*), 7.43 (ddd, $J = 7.5$, 7.5, 1.9 Hz, 2H, Ar*H*), 7.46 (ddd, $J = 7.5$, 7.5, 1.9 Hz, 2H, Ar*H*), 7.65 (s, 2H, Ar*H*), 7.67 (s, 2H, C*H* = C*H*), 7.76 (dd, $J = 7.5$, 1.9 Hz, 2H, Ar*H*), 7.86 (dd, $J = 7.5$, 1.9 Hz, 2H, Ar*H*), 8.10 (s, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 124.1, 125.2, 125.6, 126.4, 126.5, 127.9, 128.5, 131.5, 133.4, 134.9, 135.9. Anal. Calcd for $C_{24}H_{20}S_2$: C, 77.37; H, 5.41. Found: C, 77.07; H, 5.26.



(*E*)-8,9-bis(4-Bromophenyl)-8-hexadecene (150) [Homocoupling with the $TiCl_4$–Zn–Py System].[319] $TiCl_4$ (19.0 g, 0.1 mol) was slowly added to anhydrous THF (400 mL) at −5 to 5° under N_2. To the resulting yellow solution, zinc (18.0 g, 0.27 mol) was added. Then pyridine (3 mL) was injected via syringe. The reaction mixture was heated to reflux before the ketone **149** (37.0 g, 0.13 mol) in THF (100 mL) was added over 1 h and the mixture was refluxed for an additional 5 h. After cooling, the solvent was removed under reduced pressure. The remaining dark solid was treated with a saturated aq. K_2CO_3 solution and was stirred overnight. The solid was removed by filtration, dried under reduced pressure at 70°, and subjected to a Soxhlet extraction with boiling light petroleum ether for three days. The extract was condensed and the residue was purified by silica gel chromatography (CH_2Cl_2). The pure product **150** crystallized on standing (28.4 g, 82%): colorless crystals, mp 103°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (t, 6H, C*H*), 1.10–1.38 (m, 20H, C*H*), 2.45 (m, 4H, α-CH_2), 6.77, 7.17 (AA'BB', 4H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 22.6, 23.6, 28.3, 29.1, 31.8, 34.2, 119.5, 137.9, 130.7, 131.3, 142.0. Anal. Calcd for $C_{28}H_{38}Br_2$: C, 62.93; H, 7.17; Br, 29.90. Found: C, 63.23; H, 7.38; Br 29.25.

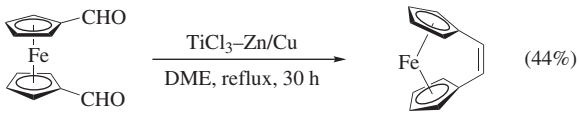


5,16-Dihydrotetrathia[22]annulene[2,1,2,1] (152) [Tandem Coupling with the $TiCl_4$–Zn–Py System].[149] A CH_2Cl_2 solution of $TiCl_4$ (1.0 M, 13.6 mL) was added to a THF (100 mL) suspension of zinc dust (1.76 g) under N_2 with stirring over 20 min. The reaction mixture was heated to reflux for 1 h, and then a THF (100 mL) solution of the dialdehyde **151** (310 mg, 1.31 mmol) and pyridine (1.76 mL) was added through a syringe over 30 min to the gently refluxing mixture. After refluxing for 18 h under N_2, the reaction was carefully quenched by addition of an aqueous solution of K_2CO_3 (10%, 24 mL). The reaction mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was extracted with CH_2C1_2 (150 mL). The extract was washed with water (2 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography ($CHCl_3$) to give **152** (210 mg, 78%): mp 153.5–155.5°; ^{1}H NMR ($CDCl_3$) δ 6.52 (s, 4H), 6.77 (s, 4H), 6.78 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 31.6, 123.5, 124.8, 128.3, 138.5, 145.2; HRMS (m/z): M^+ calcd for $C_{22}H_{16}S_4$, 408.0135; found, 408.0137.



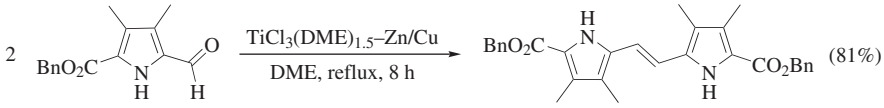
(+)-Aristoteline (119) [Intramolecular Coupling with the $TiCl_3$–Zn System by the "Instant Method"].[7] A suspension of the oxo amide **153** (24 mg, 0.074 mmol), $TiCl_3$ (45 mg, 0.29 mmol), and zinc (77 mg, 1.18 mmol) in THF (2 mL) was heated to reflux for 4 h. EDTA (430 mg, 1.47 mmol) was added, and the mixture was stirred for 1 h at rt, diluted with THF (20 mL), and filtered through a short plug of silica. The filtrate was condensed and the residue was purified by chromatography (hexane/EtOAc/Et_3N, 10:10:1) to afford **119** as colorless crystals (16.2 mg, 75%): mp 160–162.5°; $[\alpha]^{20}_D + 20.2$ (c 0.3, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.31 (s, 3H), 1.53 (s, 3H), 1.20–1.71 (m, 5H), 1.90–1.93 (m, 1H), 1.95 and 2.05 (ddAB, J = 3.2, 14 Hz, 2H), 2.22–2.31 (m, 1H), 2.65 (d, J = 16.5 Hz, 1H), 3.07 (dd, J = 16.5, 5.8 Hz, 1H), 3.63 (dd, J = 1, 5.6 Hz, 1H), 7.05 (dt, J = 1.1, 7.2 Hz, 1H), 7.10 (dt, J = 1.1, 7.2 Hz, 1H), 7.29 (dd, J = 1, 8 Hz, 1H), 7.44 (dd, J = 1, 8 Hz, 1H), 7.77 (br s, 1H,

$-NH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 25.5, 27.5, 27.8, 28.6, 29.1, 33.2, 35.7, 36.0, 39.4, 50.6, 53.6, 104.4, 110.5, 118.2, 119.2, 121.1, 128.2, 136.2, 142.5.



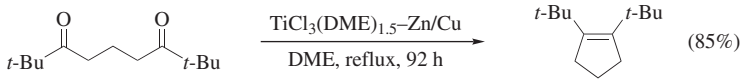
154 **108**

***ansa*-(Vinylene)ferrocene (108) [Intramolecular Coupling with the $TiCl_3$–Zn/Cu System].**[238] A 250-mL, round-bottomed Schlenk flask equipped with a magnetic stir bar was charged with $TiCl_3$ (3.50 g, 22.7 mmol), Zn/Cu (3.42 g, 5.16 mmol), and DME (~80 mL). The resulting blue-green suspension was heated to reflux for 1.5 h to give a green-brown slurry. 1,1′-Ferrocenedicarbaldehyde (**154**) (0.50 g, 2.06 mmol) in DME (10 mL) was added under reflux through a septum at the top of the condenser over 20 h using a mechanical syringe pump under reflux. After completion of the addition, the reaction mixture was heated at reflux for an additional 10 h. The red-brown suspension was allowed to cool and was filtered through a pad of 200–400 mesh Florisil to give an orange-red solution. The DME was removed by vacuum transfer and the crude product was sublimed under reduced pressure at 45° to give **108** as a bright red crystalline powder (0.192 g, 44%): ^1H NMR (400 MHz, C_6D_6) δ 3.67 (t, $J = 1.6$ Hz, 4H), 4.66 (t, $J = 1.6$ Hz, 4H), 6.09 (s, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 67.9 (C_β), 75.3 (C_α), 89.5 (*ipso*), 135.9 (CH=CH). Anal. Calcd for $C_{12}H_{10}Fe$: C, 68.62; H, 4.80. Found: C, 68.16; H, 4.99.



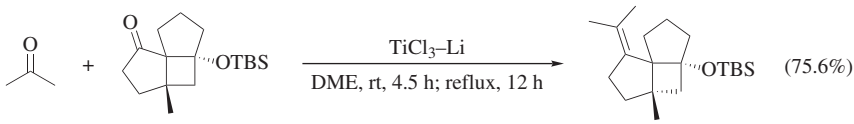
155 **77**

***trans*-1,2-bis(5-(Benzyloxycarbonyl)-3,4-dimethyl-2-pyrrolyl)ethene (77) [Homocoupling with the $TiCl_3(DME)_{1.5}$–Zn/Cu System].**[210] $TiCl_3(DME)_{1.5}$ (5.2 g, 17.9 mmol) and Zn/Cu (4.9 g, 69 mmol) were placed in a dry N_2-filled flask in a dry box. DME (100 mL) was added and the resulting mixture was heated to reflux for 2 h under N_2 to yield a black suspension. A solution of the formylpyrrole **155** (1.12 g, 4.36 mmol) in DME (10 mL) was added, and the mixture was heated to reflux for 8 h. After being cooled to rt, the reaction mixture was filtered through a glass bed of neutral alumina (CH_2Cl_2). The filtrate was condensed to afford **77** (0.853 g, 81%): mp 208–210°; ^1H NMR ($CDCl_3$) δ 2.06 (s, 6H), 2.27 (s, 6H), 5.33 (s, 4H), 6.60 (s, 2H), 7.38 (m, 10H), 8.79 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 9.2, 10.6, 65.8, 114.3, 128.1, 128.6, 161.4; HRMS (m/z): M^+ calcd for $C_{30}H_{30}N_2O_4$, 482.2205; found, 482.2184. Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.64; H, 6.17; N, 5.71.



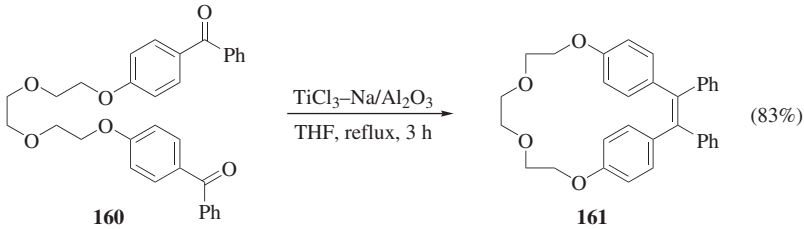
156 **157**

1,2-Di-*tert*-butylcyclopentene (157) [Intramolecular Coupling with the $TiCl_3(DME)_{1.5}$–Zn/Cu System].[320] DME (300 mL) was added to a mixture of $TiCl_3(DME)_{1.5}$ (21.59 g, 74.59 mmol) and Zn/Cu (17.0 g). After the mixture was heated to reflux for 1.5 h, 2,2,8,8-tetramethylnonane-3,7-dione (**156**) (10.00 g, 47.10 mmol) in DME (50 mL) was added via cannula. The mixture was heated to reflux for 92 h, cooled to rt, and hexane (200 mL) was added. The mixture was filtered through a glass frit in air and the solvent was removed. The residual murky oil was purified by silica gel column chromatography (hexane) to afford **157** as a colorless oil (7.20 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 18H), 1.50 (q, $J = 7.69$ Hz, 2H), 2.49 (t, $J = 7.69$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 32.5, 33.8, 39.1, 141.4. Anal. Calcd for $C_{13}H_{24}$: C, 86.59; H, 13.41. Found: C, 85.75; H, 13.63.

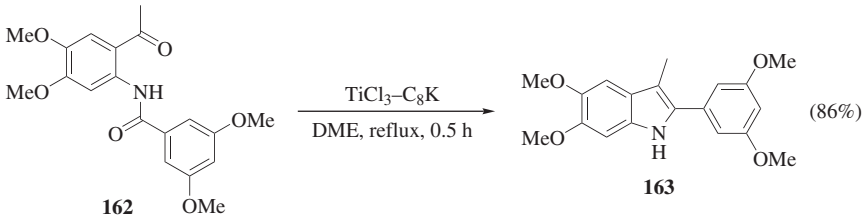


158 **159**

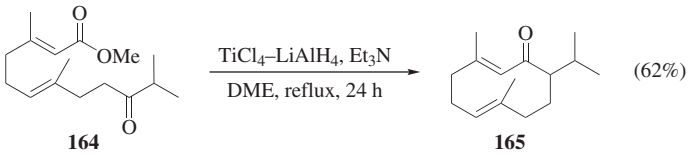
1-Isopropylidene-3a-methyl-4a-(*tert*-butyldimethylsiloxy)-2,3,3a,4,4a,5,6,7-octahydrocyclobuta[1,2:1,4]dicyclopentene (159) [Mixed-Coupling with the $TiCl_3$–Li System].[321] A slurry of lithium wire (0.90 g, 0.13 mol) and $TiCl_3$ (5.74 g, 0.15 mol) in DME (60 mL) was heated to reflux for 1 h under Ar. The mixture was cooled to rt and a solution of the cyclopentanone **158** (291.2 mg, 0.908 mmol) in anhydrous acetone (0.54 mL) was added over 4 h by a motor-driven syringe. After stirring for 30 min at rt, the mixture was heated to reflux for 12 h, cooled to rt, diluted with pentane (80 mL), and filtered through a pad of Florisil. The residue was washed with pentane (2 × 80 mL). Methanol was added slowly to the filtrate until gas evolution ceased to decompose any active Ti-species. The resulting black solution was passed through a pad of Florisil and the pad was washed with pentane. The combined filtrates were washed with water (200 mL) and then brine (200 mL), and dried. The solvent was evaporated and the residual pale-green oil was chromatographed on silica gel (pentane) to give **159** (239.8 mg, 75.6%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.02 (CH_3Si), 0.04 (CH_3Si), 0.86 (CH_3CSi), 0.93 (CH_3), 1.64 (d, $J = 1.5$ Hz, $CH_3C=$), 1.69 (d, $J = 1.6$ Hz, $CH_3C=$), 1.56–2.40 (m, 12H); ^{13}C NMR ($CDCl_3$) δ −2.9 (q), −2.5 (q), 17.9, 20.9 (q), 22.5 (q), 22.9 (q), 24.8 (t), 25.8 (3 x q), 30.9 (t), 32.3 (t), 40.9, 41.4 (t), 42.0 (t), 47.0 (t), 62.7, 82.3, 123.2, 139.1; HRMS (m/z): M^+ calcd for $C_{20}H_{36}OSi$, 320.2536; found, 320.2519.



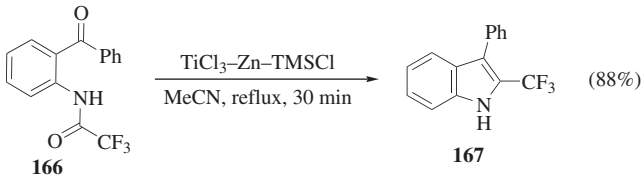
l5,16-Diphenyl-l,4,7,10-tetraoxa(10.2)[20]paracyclophan-15-ene (161) [Intramolecular Coupling with the $TiCl_3$–Na/Al_2O_3System].[85] $TiCl_3$ (1.05 g, 6.8 mmol) was added to a THF (50 mL) suspension of Na/Al_2O_3 (10%, 3.56 g, 13.6 mmol of sodium), and the mixture was heated to reflux for 1 h. A THF (20 ml) solution of diketone **160** (583 mg, 1.14 mmol) was then added dropwise over 2 h to the boiling mixture and reflux was continued for another 1 h. After being cooled to rt, the mixture was filtered and the insoluble materials were rinsed with THF (3 × 20 mL). The filtrate was evaporated and the residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford **161** as colorless crystals (451 mg, 83%): mp 184.6°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.56 (s, 4H), 3.70 (dd, $J = 4.3$, 4.7 Hz, 4H), 4.23 (dd, 4H), 6.69 and 6.85 (AB, $J = 10$ Hz, 8H), 7.10 (s, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4, 70.5, 71.4, 115.1, 126.4, 127.6, 127.9, 131.2, 132.3, 137.3, 140.6, 142.9, 157.1. Anal. Calcd for $C_{32}H_{30}O_4$•H_2O: C, 74.70; H, 6.66. Found: C, 74.73; H; 6.50.



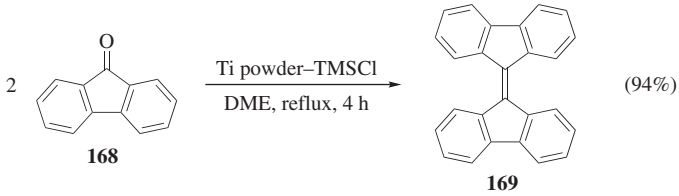
2-(3,5-Dimethoxyphenyl)-5,6-dimethoxy-3-methylindole (163) [Intramolecular Coupling with the $TiCl_3$–C_8K System].[82] $TiCl_3$ (1.58 g, 10.2 mmol) was added to a DME (50 mL) suspension of C_8K (4.2 g, 31 mmol), and the resulting suspension was heated to reflux for 1.5 h. The oxo amide **162** (310 mg, 0.9 mmol) in DME (15 mL) was added and heating was continued for 0.5 h. The suspension was filtered through a plug of silica gel, the graphite was washed with EtOAc (50 mL in several portions), the combined filtrates were concentrated, and the residue was purified by silica gel column chromatography to afford **163** as colorless crystals (240 mg, 86%): mp 141–142°; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 3H, CH_3), 3.84, 3.85, 3.88, 3.97 (s, 3H each, OCH_3), 6.45 (s, 1H, ArH), 6.71 (s, 2H, ArH), 6.84 (s, 1H, ArH), 7.02 (s, 1H, ArH), 8.06 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.1, 55.6, 56.4, 56.7, 94.7, 99.1, 101.2, 105.8, 109.0, 123.1, 130.4, 132.9, 135.7, 145.3, 147.7, 161.2. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.65; H, 6.60; N, 4.20.



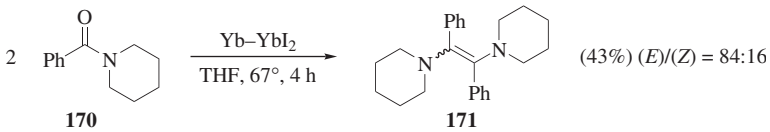
(±)-Acoragemacrone (165) [Intramolecular Coupling of a Keto Ester with the $TiCl_3$–$LiAlH_4$ System].[322] $LiAlH_4$ (80 mg, 2.06 mmol) was added to a suspension of $TiCl_3$ (640 mg, 4.16 mmol) in freshly distilled DME (25 mL) at 0° under Ar with stirring. After 5 min, anhydrous triethylamine (0.3 mL, 2.15 mmol) was added to the mixture and the slurry was heated to reflux for 2 h. A DME (20 mL) solution of the α,β-unsaturated oxo ester **164** (75 mg, 0.28 mmol) was slowly added by syringe over 20 h, the mixture was heated at reflux for an additional 4 h, cooled to 0°, diluted with Et_2O (15 mL), and quenched by addition of MeOH (5 mL) and water (5 mL). The mixture was passed through a short column of silica gel and the filtrate was washed with brine and dried. After removal of the solvent under reduced pressure, the residual oil was purified by flash column chromatography on silica gel (pentane/ether, 30:1) to give **165** as colorless oil (38 mg, 62%): ^{1}H NMR ($CDCl_3$) δ 0.87 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 1.24 (d, $J = 1.2$ Hz, 3H), 1.96 (d, $J = 1.1$ Hz, 3H), 1.50–2.40 (br m, 10H), 4.90–5.10 (br m, 1H), 5.71 (br s, 1H); EIMS (m/z): M^+ 220 (15), 205 (24), 177 (19), 149 (23), 121 (22), 107 (31), 81 (69), 69 (14), 43 (100).



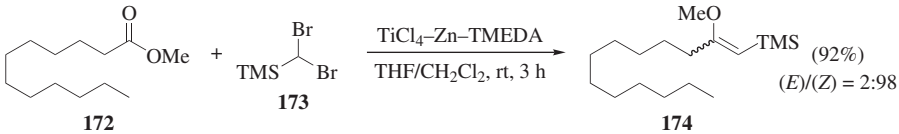
3-Phenyl-2-trifluoromethylindole (167) [Intramolecular Coupling with the Catalytic $TiCl_3$–Zn–TMSCl System].[83] TMSCl (2.29 g, 21.04 mmol) was added via syringe to a suspension of the oxo amide **166** (1.23 g, 4.19 mmol), $TiCl_3$ (65 mg, 10 mol %), and zinc dust (1.37 g, 21.04 mmol) in MeCN (18 mL). The mixture was heated at reflux for 30 min, cooled, diluted with EtOAc (25 mL), and filtered through a pad of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to give **167** (961 mg, 88%) as pale yellow crystals: mp 63–64°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (td, $J = 7.5$, 1.3 Hz, 1H), 7.32–7.56 (m, 7H), 7.64 (d, $J = 8.0$ Hz, 1H), 8.45 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.7, 119.9, 121.1, 121.2 (q, $J = 37$ Hz), 121.3, 121.7 (q, $J = 167$ Hz), 125.1, 127.4, 127.6, 128.4, 130.0, 132.2, 135.0; MS (m/z): M^+ 261 (100), 240 (12), 222 (10), 221 (11).



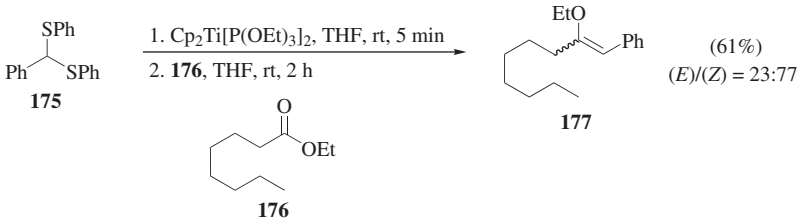
9,9-Bisfluorenylidene (169) [Homocoupling with the Commercial Titanium Powder–TMSCl System].[83] TMSCl (2.0 mL, 11.6 mmol) was added to a suspension of titanium powder (0.793 g, 16.55 mmol) in DME (10 mL). The mixture was heated at reflux for 67 h and then 9-fluorenone (**168**) (0.911 g, 5.06 mmol) was added to the boiling suspension in one portion. After being heated at reflux for 4 h, the mixture was cooled to rt and filtered through a short pad of silica gel. The insoluble residue was rinsed with THF in several portions (~100 mL) and the combined filtrates were concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 10:1) to give **169** (0.780 g, 94%) as orange-red crystals: mp 187–189°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15–7.35 (m, 8H), 7.68 (dd, $J = 7$, 1 Hz, 4H), 8.37 (d, $J = 4$ Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.87, 126.71, 126.83, 129.13, 138.25, 141.00, 141.30; MS (m/z): M^+ 328 (100), 162 (23).



1,2-Dipiperidinostilbene (171) [Homocoupling with the Yb–YbI_2 System].[108] Ytterbium powder (0.7 mmol), 1,2-diiodoethane (0.3 mmol), and THF (3 mL) were placed in a 20-mL, two-necked flask equipped with a condenser under Ar. The mixture was heated to 67° for 1 h with stirring to generate the Yb–YbI_2 reagent. 1-Benzoylpiperidine (**170**) (0.5 mmol) was added, and the resulting mixture was stirred at 67° for 4 h. Saturated aq $NaHCO_3$ solution (40 mL) was added, and the products were extracted with Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (basic Al_2O_3, activity I, Merck Art. 02069 containing 15 wt % of water, hexane) to give **171** as a yellow solid (0.11 mmol, 43%, (E)/(Z) = 84:16): mp 112.0–112.5°; ^{1}H NMR (270 MHz, $CDCl_3$) [(E)-isomer] δ 1.27 (br s, 12H), 2.29 (br s, 8H), 7.05–7.19 (m, 2H), 7.19–7.35 (br d, 8H); [(Z)-isomer] δ 1.50 (br s, 12H), 2.91 (br s, 8H), 6.83–6.97 (m, 6H), 6.97–7.05 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) [(E)-isomer] δ 24.4, 27.2, 52.9, 126.2, 127.6, 129.7, 136.5, 142.4; [(Z)-isomer] δ 24.8, 27.0, 51.9, 125.4, 127.1, 131.3, 137.7, 140.6. Anal. Calcd for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08. Found: C, 82.99; H, 8.69; N, 8.02.



2-Methoxy-1-(trimethylsilyl)tridec-1-ene (174) [Carbonyl Olefination with the CH_2X_2–Zn–$TiCl_4$ System].[162] A CH_2Cl_2 solution of $TiCl_4$ (2.0 M, 4.0 mmol) was added at 0° to a mixed solvent of THF (1.5 mL) and CH_2Cl_2 (6 mL) under Ar. TMEDA (8 mmol) was added to the yellow solution at rt and the mixture was stirred at rt for 15 min. Zinc dust (9.0 mmol) was added and the resulting mixture was stirred at rt for 30 min. The color of the suspension turned from brownish-yellow to dark greenish-blue in a slightly exothermic process. The ester **172** (1.0 mmol) and $TMSCHBr_2$ (**173**) (2.2 mmol) in CH_2Cl_2 (1 mL) were added to the mixture. The color of the mixture gradually turned dark reddish-brown. After being stirred at rt for 3 h, THF (10 mL) was added. The mixture was cooled to 0° and a saturated aq. K_2CO_3 solution (2.0 mL) was added. After being stirred at 0° for another 1 h, the mixture was diluted with ether/Et_3N (200:1, 10 mL) and then passed rapidly through a short column of basic alumina (activity III). The solution was concentrated and the resulting white solid was removed by filtration with the aid of Hyflo Super-Cel[R] using hexane/Et_3N 200:1, (50 mL) as an eluent. The filtrate was concentrated and the crude product was purified by column chromatography on basic alumina (activity III, hexane/Et_3N, 200:1) to give **174** (92%, $(E)/(Z) = 2:98$): bp 60° (bath temp, 1.0 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9H), 0.88 (t, $J = 7$ Hz, 3H), 1.20–1.70 (m, 18H), 2.16 (t, $J = 7$ Hz, 2H), 3.48 (s, 3H (E)), 3.51 (s, 3H (Z)), 4.00 (s, 1H (E)), 4.30 (s, 1H (Z)). Anal. Calcd for $C_{17}H_{36}OSi$: C, 71.75; H, 12.75. Found: C, 71.72; H, 13.01.



2-Ethoxy-1-phenylnon-1-ene (177) [Carbonyl Olefination with the $RCH(SPh)_2$–$Cp_2Ti[P(OEt)_3]_2$ System].[170] To a flask charged with finely powdered 4 Å molecular sieves (200 mg), Mg turnings (58 mg, 2.4 mmol), and Cp_2TiCl_2 (498 mg, 2 mmol) were added THF (4 mL) and $P(OEt)_3$ (0.68 mL, 4 mmol) with stirring at rt under Ar. After 3 h, a solution of α,α-bis(phenylthio) toluene (**175**) (170 mg, 0.55 mmol) in THF (1 mL) was added to the THF solution of the resulting $Cp_2Ti[P(OEt)_3]_2$ and the reaction mixture was further stirred for 5 min. Then a solution of ethyl caprylate (**176**) (86 mg, 0.5 mmol) in THF

(2.5 mL) was added dropwise over 10 min. After stirring the reaction mixture for 2 h, the reaction was quenched by the addition of 1 M aqueous NaOH solution (30 mL) and the insoluble materials were removed by filtration through celite. The filtrate was extracted with Et_2O and the extract was dried (K_2CO_3). After removal of the solvent, the residue was purified by column chromatography (Merck aluminum oxide 90, Brockmann III, hexane) to give **177** (75 mg, 61%, $(E)/(Z) = 23:77$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–0.94 (m, 3H), 1.21–1.41 (m, 1H), 1.49–1.62 (m, 2H), 2.27 (t, $J = 7.6$ Hz, 1.54H), 2.30 (t, $J = 7.8$ Hz, 0.46H), 3.83 (q, $J = 6.8$ Hz, 0.46H), 3.90 (q, $J = 6.8$ Hz, 1.54H), 5.40 (s, 0.77H), 5.54 (s, 0.23H), 7.05–7.31 (m, 3.46H), 7.65 (m, 1.54H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.7, 15.5, 22.7, 27.7, 27.8, 29.1, 29.2, 29.3, 29.4, 31.0, 31.8, 32.8, 62.4, 63.4, 99.6, 108.3, 125.0, 125.3, 128.0, 128.1, 128.7, 136.8, 138.1, 156.9, 159.5; HRMS (m/z): M^+ calcd for $C_{17}H_{26}O$, 246.1984; found, 246.1990.

TABULAR SURVEY

The tables are organized by type of reaction (homocoupling, mixed-coupling, intramolecular coupling, and tandem coupling) and by carbonyl compounds (aldehydes, ketones, or carboxylic acid derivatives). Within each table, entries are listed in the order of increasing number of carbons of the carbonyl compounds. In the case of mixed-couplings between aldehydes and ketones, entries are ordered based on the number of the carbons of the aldehydes. In all tables, reaction condition 1 denotes the source of low-valent metal reagent, reducing agent, solvent, and the conditions for the generation of the low-valent metal reagent. In Tables 1A, 1B, 1C, 2A, 2B, and 2C, conditions 2 indicate conditions for the coupling of the carbonyl compounds. In Tables 2D, 3A, 3B, 3C, 3D, 4A, and 4B, conditions 2 indicate the reaction conditions for addition of the carbonyl compounds and conditions 3 represent conditions for the coupling of the carbonyl compounds. An em-dash (—) in the "Conditions" column means that reaction conditions were not given and an em-dash (—) in the "Product(s) and Yield(s) (%)" column means that yields were not reported. The computerized literature survey was conducted using SciFinder, Web of Science, PubMed, and ScienceDirect with several search headings, and the literature coverage is from 1973 to mid 2010. Coupling reactions reported in patents are not included in the tables. Our apologies are extended to the authors whose work has been inadvertently omitted.

The following abbreviations (not included in *The Journal of Organic Chemistry* Standard Abbreviations and Acronymns) are used in the Tabular Survey:

DPMS	diphenylmethylsilyl
Np	naphthyl
PGC	process gas chromatography
SCE	saturated calomel electrode
TES	triethysilyl
TBDPS	*tert*-butyldiphenylsilyl
Tol	tolyl

TABLE 1A. HOMOCOUPLING OF ALDEHYDES

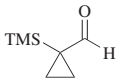
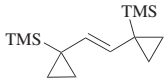
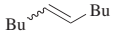
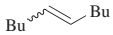
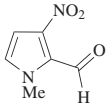
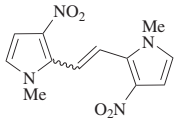
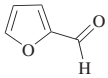
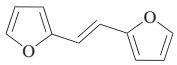
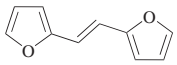
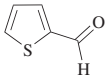
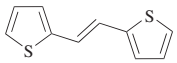
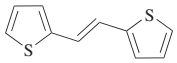
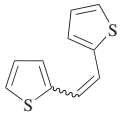
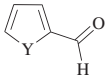
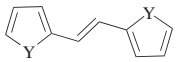
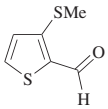
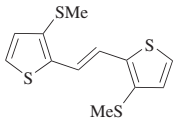
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3			
	1. $TiCl_3(THF)_3$, Mg, THF, 40°, 1 h 2. 40°, 1.5 h	(30) + (30)	4
	WCl_5, $LiAlH_4$, THF, rt, 6 h	(18)	45
C_4			
	1. $TiCl_3$, Li, DME, reflux, 16 h 2. rt, 2 h; then reflux, 20 h	 (38)	43
C_5			
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (77), (*E*)/(*Z*) = 70:30	27, 62
	$InCl_3$, Zn, MeCN, reflux, 9 h	 (70), (*E*)/(*Z*) = 70:30	104
	$TiCl_4$, Zn, THF, py, reflux 1.5 h	 (7)[a]	125
	$TiCl_2(THF)_2$, THF, reflux, 24 h	 (95)	34
	$TiCl_4$, Zn	 (—)	323
	$TiCl_4$, Zn, THF, reflux	 Time (h): 4 (71); 3.5 (98)	324 325, 326
	—	 (—)	327
	$Ti(O\textit{i}\text{-}Pr)_4$, Mg, TMSCl, Et_3N, THF, 40°, 72 h	 (53), (*E*)/(*Z*) = 10:90	87
	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 15 h	 Y: S (91); EtO_2CN (30); MeO_2CN (50)	124
	1. $TiCl_4$, Zn, py, THF, reflux, 1.5 h 2. Reflux, 5 h	 (55)	328

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

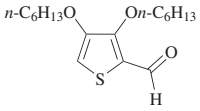
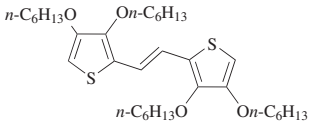
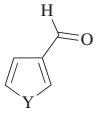
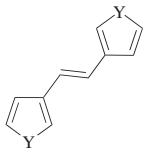
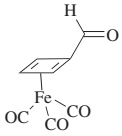
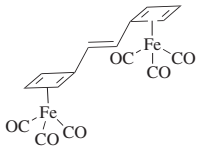
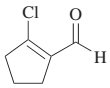
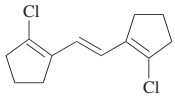
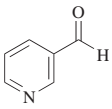
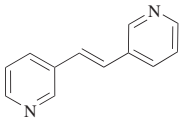
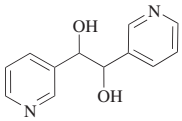
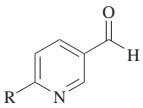
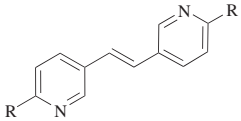
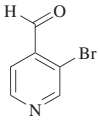
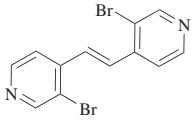
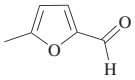
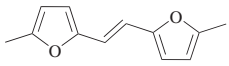
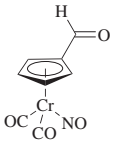
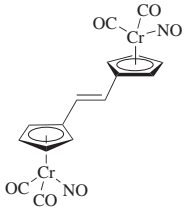
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5			
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Py, reflux, 2 h	 (76)	329
	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 15 h	 Y S (93) O (45)	124
	1. $TiCl_3$, $LiAlH_4$, THF, rt, 10 min 2. Reflux, 4 h	 (56)	207
C_6			
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 1 h; then rt, 4 h; then reflux, 2 h	 (50)	44
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 15 h	 (28) +  (24)	124
	1. $TiCl_4$, Zn, py, dioxane, 80°, 2 h 2. 80°, 12 h	 R MeO (40) MeS (30)	212
	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 15 h	 (30)	124
	$TiCl_3$, $LiAlH_4$, THF, reflux	 (52)	330
	1. $TiCl_4$, $LiAlH_4$, THF, 90°, 12 h 2. 55°, 16 h	 (36)	205

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

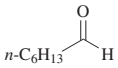
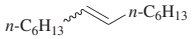
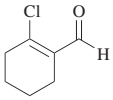
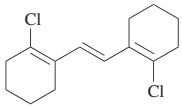
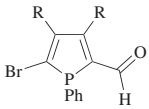
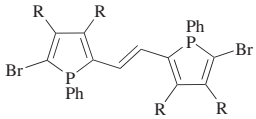
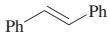
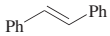
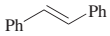
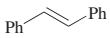
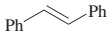
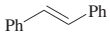
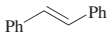
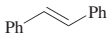
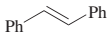
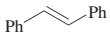
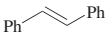
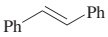
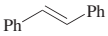
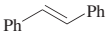
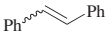
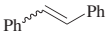
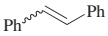
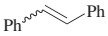
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 18 h	(52)	114
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 5.5 h	 (47)	67
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 30 min; then reflux, 3 h	 (70)	44
C_{7-17}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 h	 R dr Me (47) — Ph (71) 90:10	126
C_7			
	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Reflux, 77 h	 (90)	83
	$TiCl_2(THF)_2$, THF, reflux, 24 h	 (98)	34
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 16 h	 (97)	27
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 2 h	 (72)	67
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 3 h	 (95)	73, 74
	$TiCl_3$, Zn, DME, reflux, 1 h	 (78)	7
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (85)	5
	1. $TiCl_4$, C_8K, THF, reflux, 30 min 2. Reflux, 1 h	 (95)	73
	$TiCl_4$, Zn, dioxane, reflux, 4 h	 (98), (*E*)/(*Z*) >99:1	3
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5°, 30 min 2. Microwave irradiation, 7 min	 (92)	121

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 20 min 2. Tertiary amine, reflux, 3 h	 Tertiary amine *n*-Bu_3N (92) Proton Ssponge[b] (92)	110
	1. $TiCl_4$, Hg/Mg, THF 2. 0°, 2 h; then reflux, 24 h	 (>95)	331
	1. $NbCl_5$, MeLi, DME, 80°, 24 h 2. Reflux, 8 h	 (100)	96
	$W_2(OCH_2CMe_3)_6(Py)_2$, hexane, 22°, 2–24 h	 (34)	99
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 2 h	 (85), (*E*)/(*Z*) = 90:10	114
	1. $TiCl_3$, Li, THF, ultrasonication, 30°, 1 h 2. Ultrasonication, 30°, 45 min	 (83)	312
	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 30 min	 (82) dr 95:5	69
	1. $TiCl_3$, $LiAlH_4$, THF, 0°, 30 min; then reflux, 10 min 2. Reflux, 20 h	 (88)	120

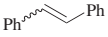
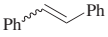
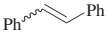
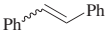
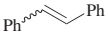
	1. $TiCl_3(THF)_3$, Mg, THF, 40°, 1 h 2. 40°, 1.5 h	 (—)	4
	$AlCl_3$, Zn, MeCN, reflux, 10 h	 (92), (*E*)/(*Z*) = 99:1	88
	$Mo(CO)_6$, rt, 24 h	 Solvent CH_2Cl_2 (5) THF (10) ether (39) dioxane (13) benzene (39) pentane (41) cyclohexane (38)	45
	W(0), CH_2Cl_2, rt, 24 h	 W(0) (*E*)/(*Z*) $W(CO)_6$ (42) 21:21 $W(CO)_5PPh_3$ (18) 9:9 $W(CO)_5NH_2C_6H_{11}$ (15) 8:7 $[W(CO)_5Cl]NEt_4$ (31) 27:4 $W(CO)_5$=C(OMe)Ph (32) 19:13	45
	WCl_5, [Reagent], rt, 6 h	 [Reagent] Solvent (*E*)/(*Z*) $LiAlH_4$ THF (78) 73:5 $LiAlH_4$ ether (23) — $LiAlH_4$ dioxane (13) — $NaAlH_4$ THF (69) — Zn THF (16) —	45

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

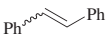
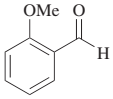
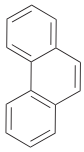
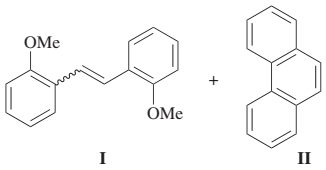
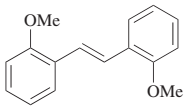
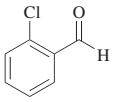
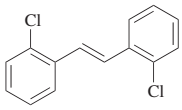
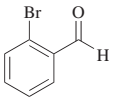
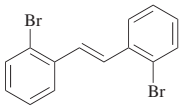
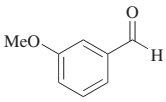
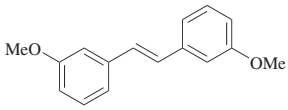
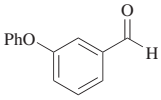
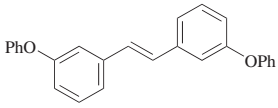
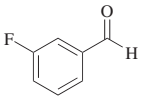
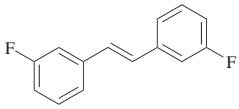
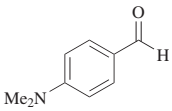
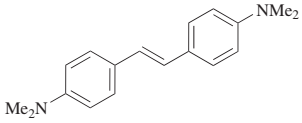
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	WCl_6, electroreduction,[c] THF, 4 h	 (96), (*E*)/(*Z*) = 91:9	103
	$TiCl_3$, Li, THF	 (25)[d]	332
	1. $TiCl_3$, Li, THF, reflux, 3 h 2. Additive, reflux, 16 h	 **I** + **II** Additive / **I** / **II**: Fullerene (35) (47); — (0) (25)	333
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 12 h 3. I_2, heptane, reflux[e]	 (10)	334
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 30 min; then reflux, 3 h	 (85)	44
	$TiCl_3$, Li, DME, reflux, 6 h	 (71)	335
	1. $TiCl_4$, Zn, THF, –10° 2. Reflux, 5 h	 (88)	233
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5°, 30 min 2. Microwave irradiation, 10 min	 (80)	121
	$TiCl_3$, Li, DME, reflux, 18 h	 (95), (*E*)/(*Z*) = 99.92:0.08	336
	$TiCl_4$, Zn, THF, reflux, 2 h	 (—)	337

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

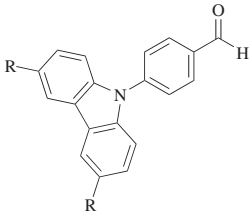
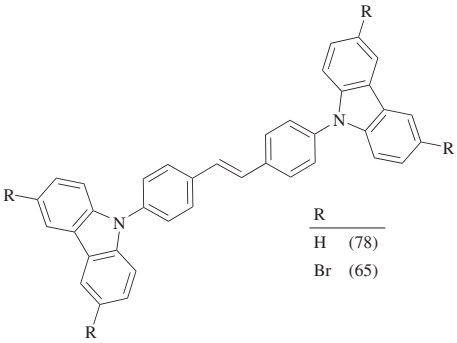
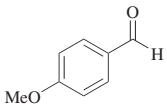
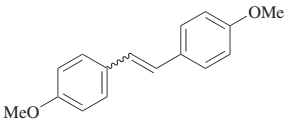
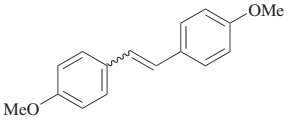
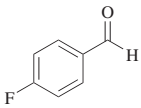
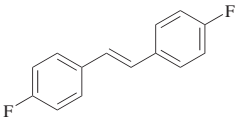
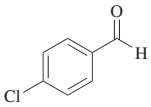
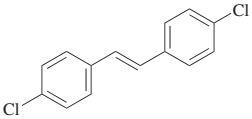
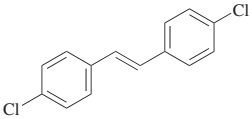
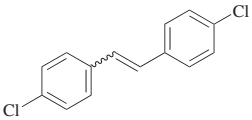
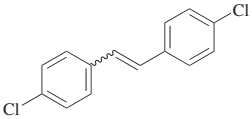
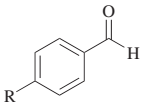
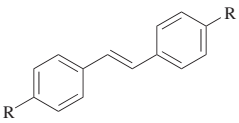
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	$TiCl_4$, Zn, dioxane	 R: H (78); Br (65)	338
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 3 h	 (68), (*E*)/(*Z*) = 60:40	67
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 14 h	 (64), (*E*)/(*Z*) = 85:15	114
	1. $TiCl_3(DME)_{1.5}$, Li, DME, reflux, 1.5 h 2. Reflux, 20 h	 (58)	339
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 2 h	 (70)	67
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5°, 30 min 2. Microwave irradiation, 5 min	 (80)	121
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 2.5 h	 (65), (*E*)/(*Z*) = 92:8	114
	$AlCl_3$, Zn, MeCN, reflux, 18 h	 (72), (*E*)/(*Z*) = 80:20	88
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2, 5 min 2. 0–5°, time	 R: H, 3 h (85); Cl, 2.5 h (82); MeO, 3.5 h (62)	115

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

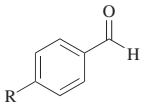
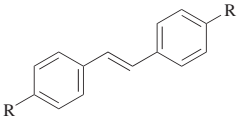
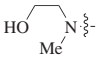
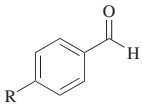
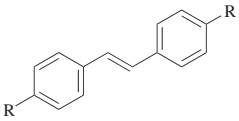
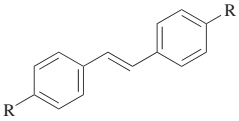
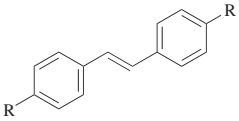
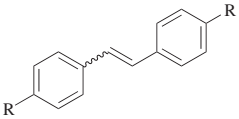
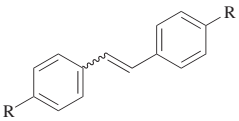
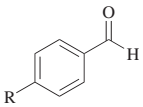
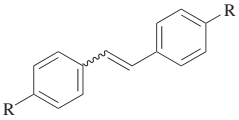
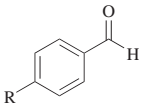
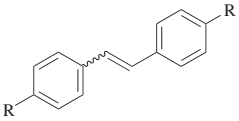
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_4$, Zn, Na, THF, reflux, 1 h 2. Reflux, 20 h	 R: Et_2N (54) R:  (50) R: (65)	340
C_{7-8}			
	$TiCl_4$, Zn, THF, 110°, microwave irradiation, 10 min	 R: H (93); *t*-BuS (87); Me (91)	317
	Zn amalgam, $ClMe_2Si(CH_2)_2SiMe_2Cl$, THF, rt, overnight	 R: H (69); MeO (79); Cl (26); Me (86)	341
	1. $ZrCl_4$, Li, DME, rt, 1 h 2. Reflux, 5 h	 R: H (86); Me (78)	93
	$Cp_2Ti(CO)_2$, THF, reflux, 10 h	 R: H (98); Cl (88); Me (99)	86
	$InCl_3$, Zn, MeCN, reflux	 R: H, 8 h (93), (*E*)/(*Z*) 98:2; Cl, 9 h (90), 86:14; Br, 8 h (75), 80:20; O_2N, 9 h (70), 70:30; Me, 7 h (88), 90:10; MeO, 8 h (80), 75:25	104
C_7			
	1. $NbCl_5$, $NaAlH_4$, THF/benzene, 0°, 10 min 2. Reflux, time	 R: H, 1 h (70), (*E*)/(*Z*) >20:1; Cl, 3 h (95), >20:1; MeO, 3 h (56), >20:1	95
C_{7-8}			
	WCl_5, $LiAlH_4$, THF, rt, 6 h	 R: Cl (65), (*E*)/(*Z*) 63:2; Me (60), 57:3; MeO (82), 76:6	45

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

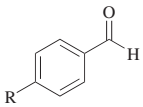
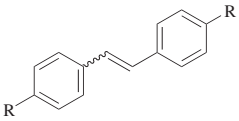
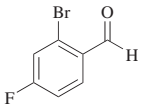
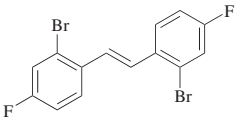
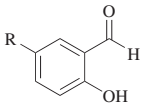
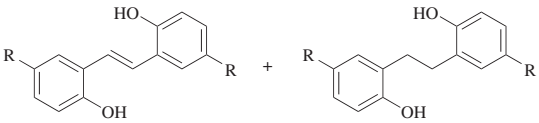
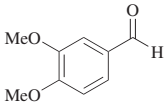
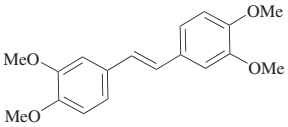
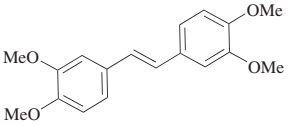
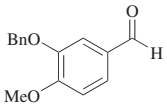
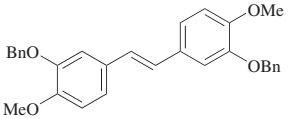
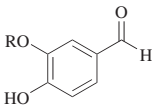
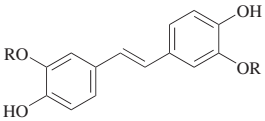
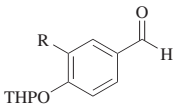
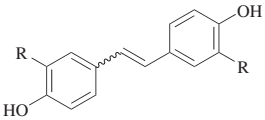
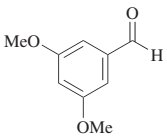
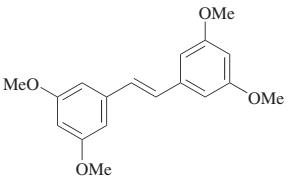
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-8}			
	$W(CO)_6$, CH_2Cl_2, rt, 24 h	 R (62) (*E*)/(*Z*) 36:26; Me (43) 29:14; MeO (63) 39:24	45
C_7			
	1. $TiCl_4$, Zn, THF, heat, 1 h 2. Reflux, 6 h	 (76)	342
C_{7-13}			
	1. $TiCl_4$, Zn, dioxane, reflux, 3 h 2. Reflux, 2 h	 **I** + **II** R: Br (83) (<1); Me (53) (30); *t*-Bu (50) (29); Ph (88) (2)	343
C_7			
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. –10 to 0°, 5.5 h	 (65)	67
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 12 h	 (65)	114
	$TiCl_4$, Zn, py, THF, reflux, 2 h	 (93)	344
	1. $TiCl_4$, Zn, THF, reflux, 40 min 2. Reflux, 3–5 h	 R: H (—); Me (—)	345
	1. $TiCl_3$, Zn, THF, reflux, 3 h 2. Reflux	 R: H (65); MeO (68)	346
	$TiCl_4$, Zn, THF, heat	 (—)	347

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

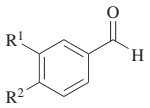
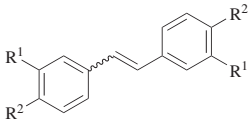
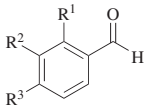
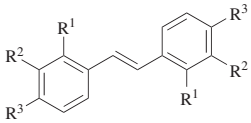
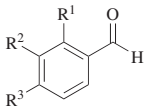
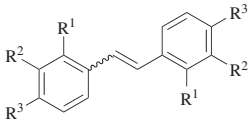
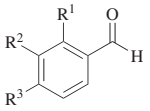
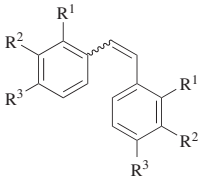
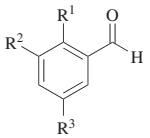
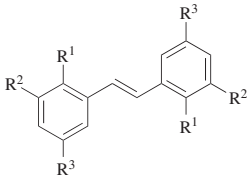
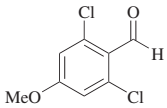
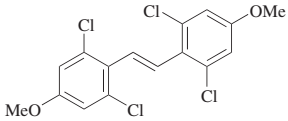
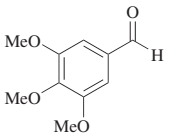
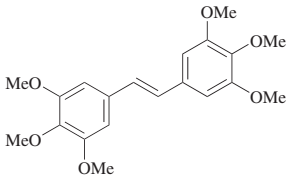
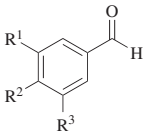
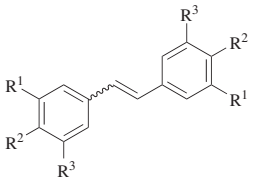
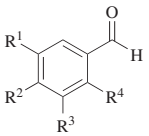
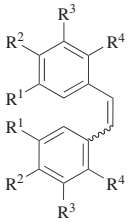
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-8} 	1. WCl_6, BuLi, THF, –78° to rt, 20 min 2. rt, 6 h		2
C_7 	1. $TiCl_3$, Li, DME, reflux, 1.5 h 2. Reflux, 18 h		348
C_{7-8} 	1. $TiCl_3$, Zn/Cu, solvent, reflux, 1 h 2. Reflux, time		349
C_7 	[bmim]Cl($AlCl_3$),[e] Zn, rt		46
	$TiCl_4$, Zn, dioxane, reflux, 3–5 h		350
	$TiCl_4$, Zn, dioxane, reflux	 (55)	351

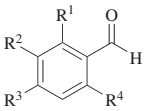
TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5°, 30 min 2. Microwave irradiation, 8 min	 (95)	121
	$TiCl_3$, Zn, THF		352
	1. $TiCl_3$, Zn, THF, reflux, 3 h 2. Reflux, 22 h		346

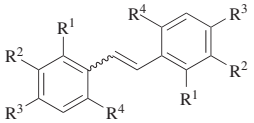
R^1	R^2	R^3		
H	HO	H	(—)	
MeO	HO	H	(—)	
HO	HO	H	(—)	
HO	H	HO	(—)	

R^1	R^2	R^3	R^4		(*E*)/(*Z*)
H	HO	H	H	(38)	30:70
MeO	HO	H	H	(36)	40:60
MeO	MeO	H	H	(72)	50:50
MeO	H	MeO	H	(70)	50:50
MeO	MeO	H	MeO	(74)	50:50

C_{7-10}



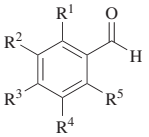
Ti(O*i*-Pr)$_4$, Mg, Et_3N, TMSCl, 40°



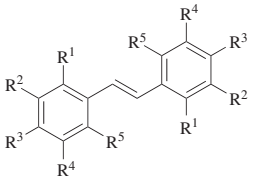
87

R^1	R^2	R^3	R^4	Time (h)		(*E*)/(*Z*)
H	H	H	H	48	(77)	87:13
MeO	H	H	H	72	(51)	91:9
H	H	MeO	H	24	(95)	99:1
H	H	Cl	H	72	(58)	61:39
H	MeO	MeO	H	48	(65)	94:6
H	H	Me	H	48	(85)	99:1
Me	H	Me	Me	24	(76)	90:10

C_{7-9}



1. $TiCl_4$, Zn/Cu (or Zn), THF
2. Reflux
3. Catalytic I_2, *o*-xylene, reflux[f]



(56-76)

R^1	R^2	R^3	R^4	R^5	
H	H	Cl	H	H	
H	H	F	H	H	
F	F	F	F	F	353
CF_3	H	H	H	H	
H	H	NC	H	H	
H	CF_3	H	CF_3	H	

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

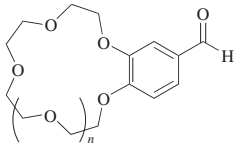
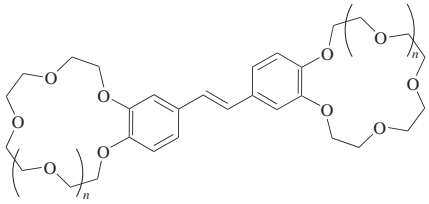
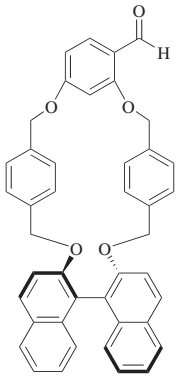
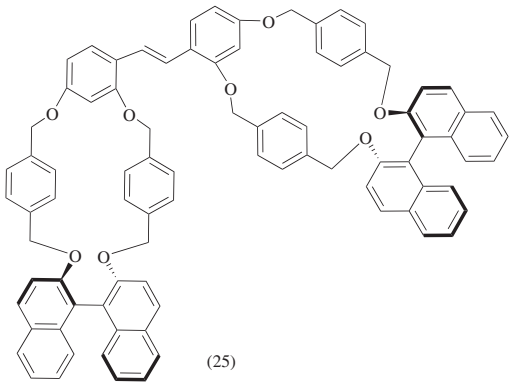
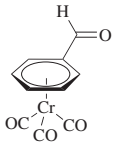
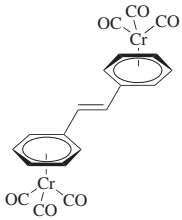
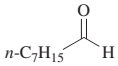
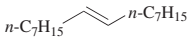
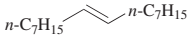
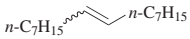
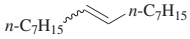
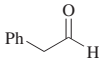
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_4$, Zn, py, THF, reflux, 30 min 2. Proton Sponge,[b] reflux, 5 h	 *n* 1 (26) 2 (31)	354
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 12 h	 (25)	237
	$NbCl_3$(DME), THF, rt, 8 h	 (78)	97
C_8			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 3 h	 (96)	73, 74
	1. $TiCl_4$, Hg/Mg, THF 2. 0°, 2 h; then reflux, 24 h	 (72)	331
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2, 5 min 2. rt, 8 h	 (80)	115
	$InCl_3$, Zn, MeCN, reflux, 9 h	 (72), (*E*)/(*Z*) = 70:30	104
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 4 h	(75)	67

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

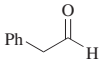
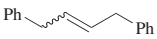
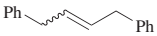
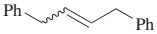
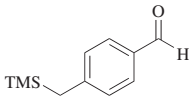
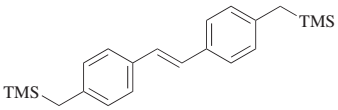
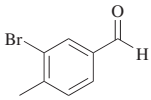
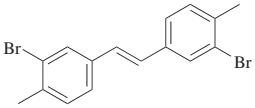
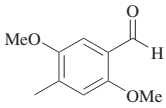
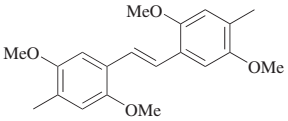
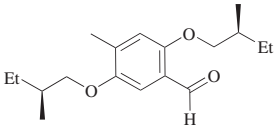
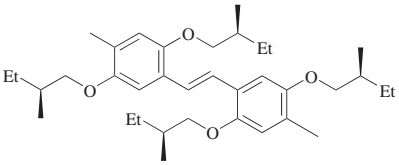
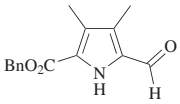
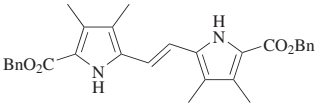
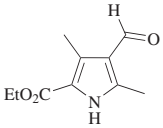
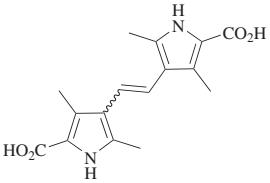
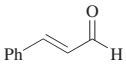
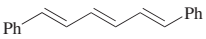
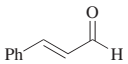
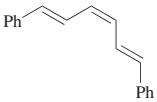
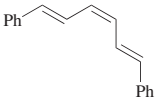
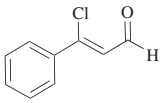
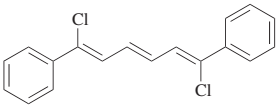
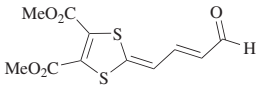
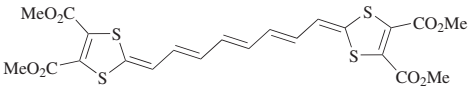
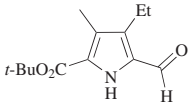
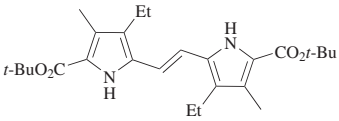
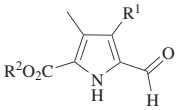
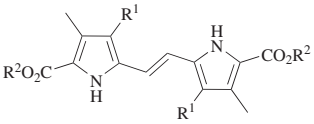
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 6 h	 (76)	114
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 16 h	 (23), (*E*)/(*Z*) = 90:10	355
	1. $TiCl_3$, Li, THF, reflux, 3 h; then, I_2 , 5 min 2. rt, 4 h	 (79)	115
	1. $TiCl_4$, Zn, DME, reflux, 1 h 2. Reflux, 20 h	 (10.7)	356
	$TiCl_4$, Zn, THF, reflux, 4 h	 (58)	357
	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 16 h	 (34)	358
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 16 h	 (31)	359
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 8 h	 (81)	210
	$TiCl_4$, Zn, THF	 (10)	211
C_9			
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5°, 30 min 2. Microwave irradiation, 5 min	 (83)	121

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

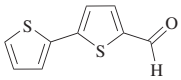
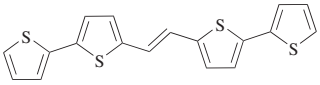
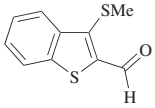
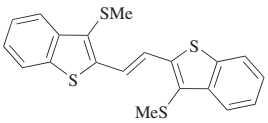
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9			
	1. $NbCl_5$, MeLi, DME, 80°, 24 h 2. Reflux, 72 h	 (26)	96
	1. $NbCl_5$, K, DME, 80°, 30 min 2. Reflux, 1 h	 (55)	96
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 30 min; then reflux, 3 h	 (79)	44
	1. $TiCl_3$, $LiAlH_4$, THF 2. Py, reflux, 2 h	 (20)	199
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 8 h	 (21.7)	210

C_{9-10}

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, overnight		209

R^1	R^2	
Et	Et	(66)
$EtO_2C(CH_2)_2$	Me	(75)
$EtO_2C(CH_2)_2$	Et	(68)
$EtO_2C(CH_2)_2$	Bn	(74)

C_9

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
	$TiCl_4$, Zn, THF, reflux, 4 h	 (63)	324
	1. $TiCl_4$, Zn, py, THF, reflux, 1.5 h 2. Reflux, 9.5 h	 (95)	328

C_{10}

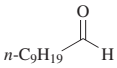
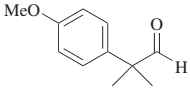
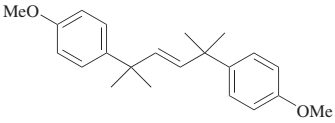
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	(60)	27
	1. $TiCl_4$, Zn, THF, py, reflux, 1 h 2. Reflux, 2 h; then addition of aldehyde; then reflux, 40 h	 (22)	360

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

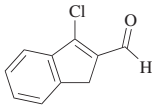
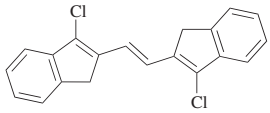
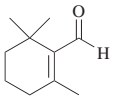
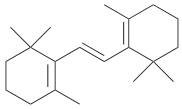
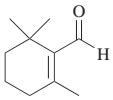
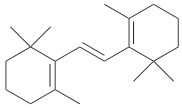
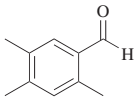
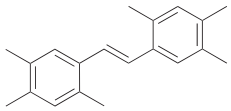
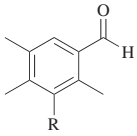
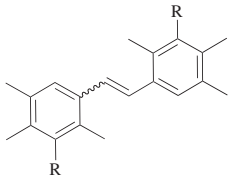
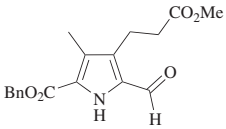
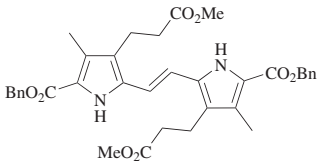
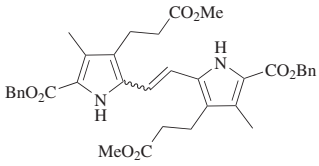
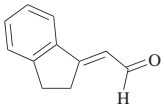
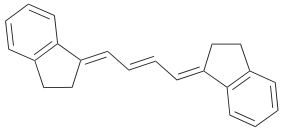
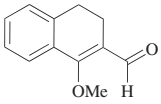
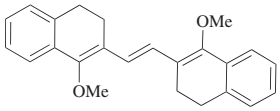
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 1 h; then rt, 2 h; then reflux, 2 h	 (60)	44
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 20 min 2. Tertiary amine, reflux, 3 h	 Tertiary amine: *n*-Bu_3N (90); Proton Sponge[b] (94)	110
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (90)	361
	$TiCl_4$, Zn, THF, reflux, 16 h	 (74)	362
C_{10-11}			
	$TiCl_4$, Zn	 R: H (—); Me (—)	363
C_{10}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 8 h	 (45.8)	210
	$TiCl_4$, Zn, THF	 (86), (*E*)/(*Z*) = 4:1	211
C_{11}			
	1. $TiCl_3$, $LiAlH_4$, THF, rt, 40 min 2. Reflux, 4.5 h	 (45)	364
	$TiCl_4$, Zn, DME	 (—)	365

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

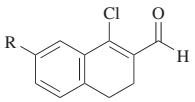
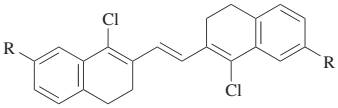
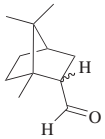
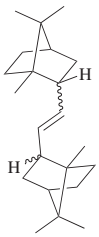
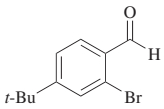
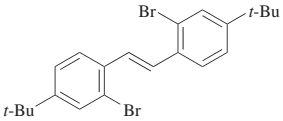
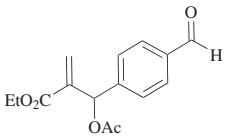
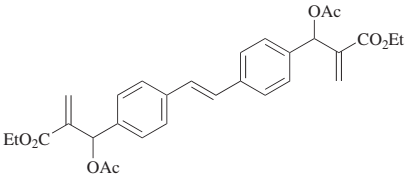
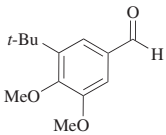
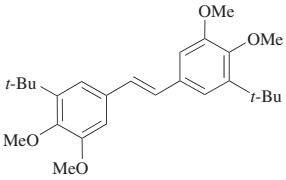
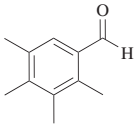
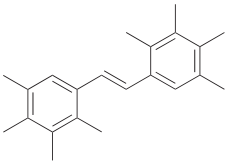
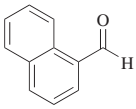
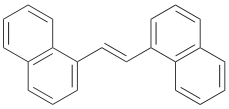
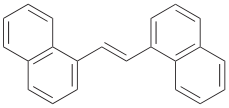
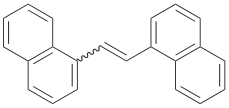
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. 0–5°, 30 min; then reflux, 4 h	 R: H (92); Br (84)	44
	$TiCl_3$, Li, THF, reflux, 40 h	 (79) ~90:10[g]	366
	$TiCl_4$, Zn, THF, reflux, 4 h	 (97)	367
	$TiCl_4$, Zn, THF, −10° to reflux, 4 h	 (86)	123
	1. $TiCl_4$, Zn, THF, reflux 2. Reflux, 24 h	 (58)	368
	$TiCl_4$, Zn, THF, reflux, 16 h	 (64)	362
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 (21)	197
	1. $TiCl_4$, Zn/Cu, THF 2. Reflux, 3 h	 (90)	369
	1. $TiCl_3(THF)_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 30 min	 (60) dr 95:5	69

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

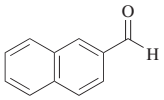
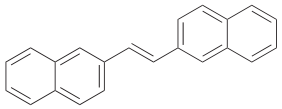
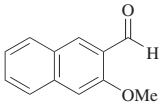
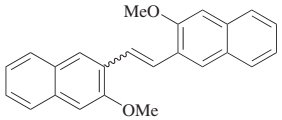
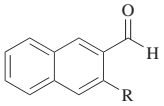
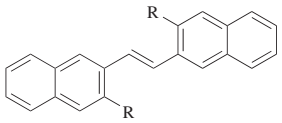
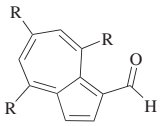
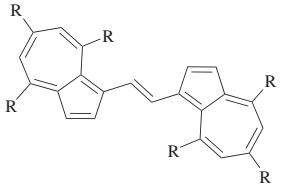
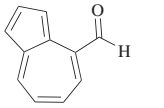
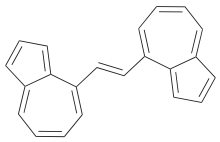
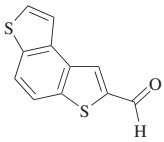
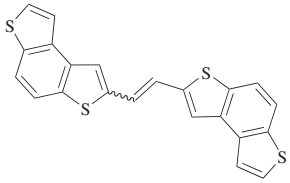
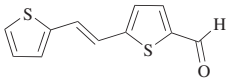
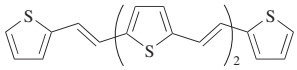
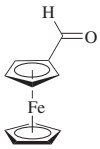
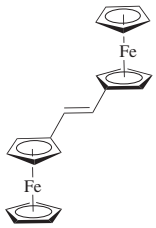
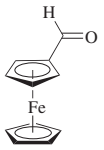
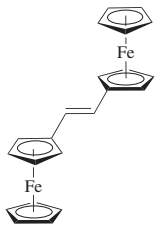
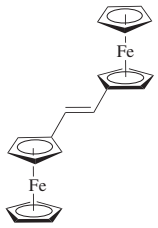
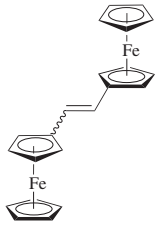
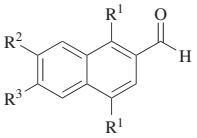
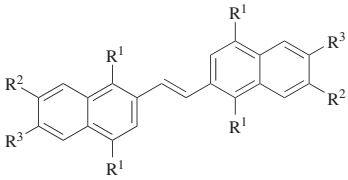
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 (33)	197
	Ti(O*i*-Pr)$_4$, Mg, TMSCl, Et_3N, THF, 40°, 48 h	 (49), (*E*)/(*Z*) = 65:35	87
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 10 h	 R: MeS (80); MeSe (77)	318
C_{11-14}			
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 R: H (68); Me (40)	197
C_{11}			
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 (61)	197
	1. $TiCl_4(THF)_2$, Zn, THF, reflux, 2 h; then py, 30 min 2. Reflux, 7 h	 (97)	370
	$TiCl_4$, Zn, THF, reflux, 4 h	 (97)	326
	$TiCl_4$, Zn, THF, reflux, 4 h	 (76)	371

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	$TiCl_4$, Zn	 (40)	47
	Zn, TMSCl, THF, 0°, 2 h	 (75)	92
	1. $TiCl_3$, $LiAlH_4$, THF, 0°, 0.5 h 2. rt, 3 h	 (25), (*E*)/(*Z*) = 3.5:1	205

C_{12-13}

	$TiCl_3$, $LiAlH_4$, THF		140

R^1	R^2	R^3	
H	Me	H	(—)
H	H	Me	(—)
Me	H	H	(—)

C_{12}

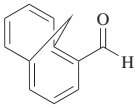
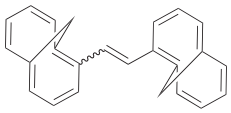
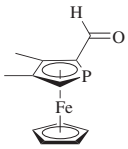
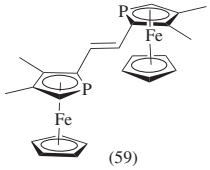
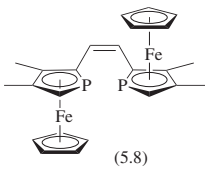
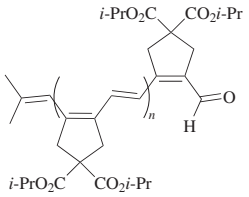
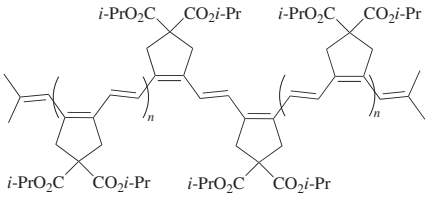
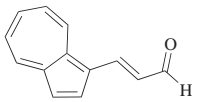
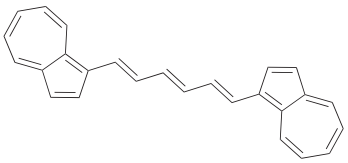
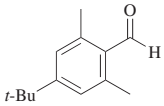
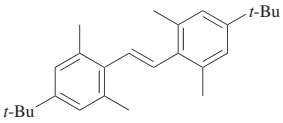
	$TiCl_4$, Zn, py, THF, reflux, 20 min	 (83)	372
	$TiCl_3(DME)_{1.5}$, Zn/Cu, py, DME, reflux 30 min	 (59) +  (5.8)	373

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-30}			
	1. $TiCl_4$, Zn, DME, reflux, 2 h 2. rt, 12 h; then reflux, 1 h	 *n*: 0 (61); 1 (82); 2 (25)	198
C_{13}			
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 (33)	197
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h; 2. Reflux, 6 h	 (75)	374

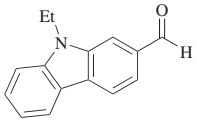
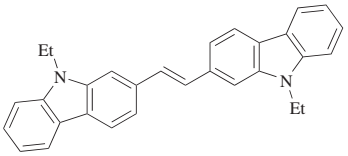
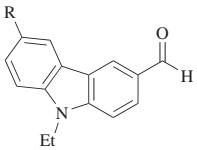
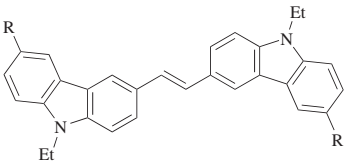
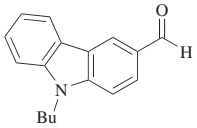
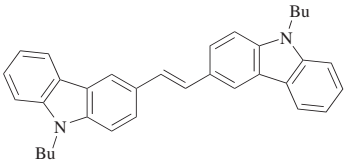
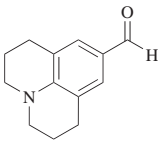
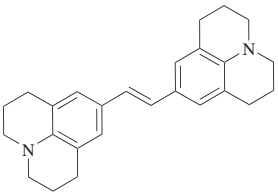
	1. $TiCl_4$, Zn, THF, 1 h 2. Reflux, 4 h	 (88)	375
	$TiCl_4$, Zn, THF, reflux, 4 h	 R: H (90); Br (85)	376
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Py, reflux, 10 h	 (58)	377
	$TiCl_4$, Zn, THF, reflux, 2 h	 (—)	337

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

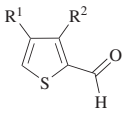
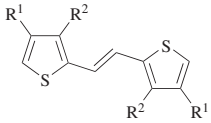
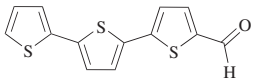
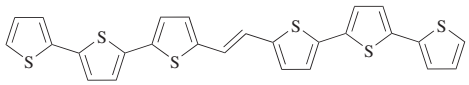
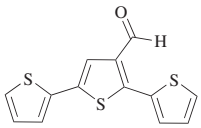
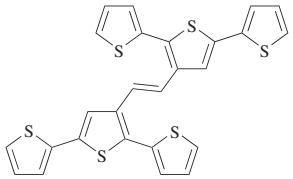
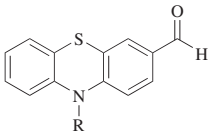
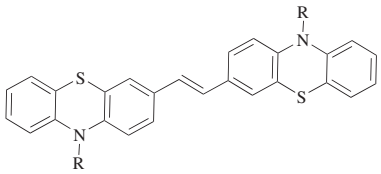
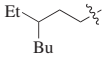
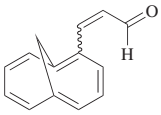
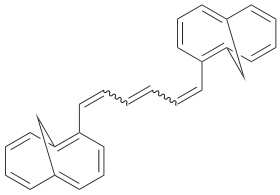
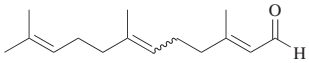
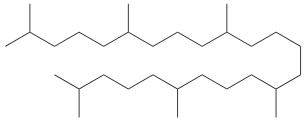
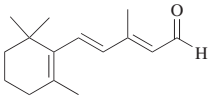
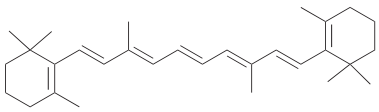
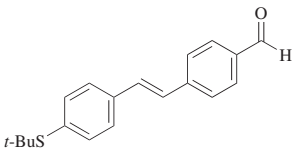
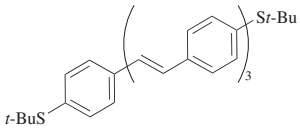
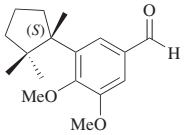
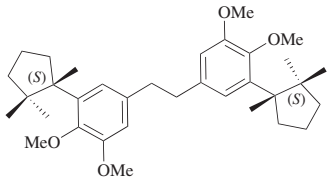
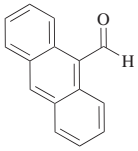
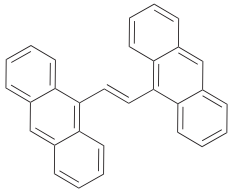
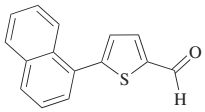
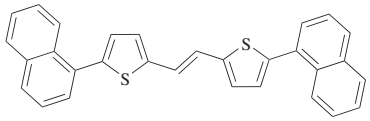
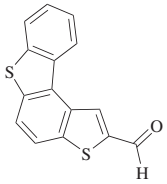
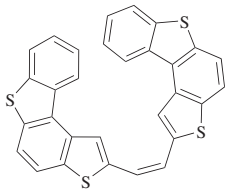
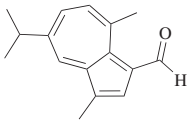
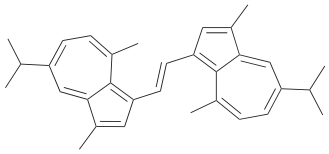
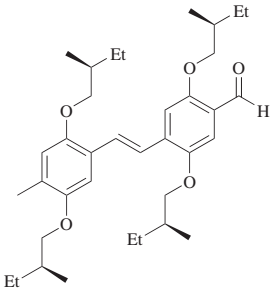
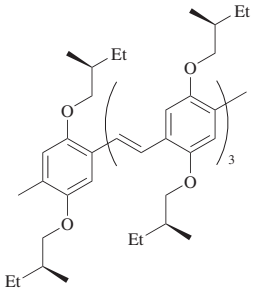
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_4$, Zn, THF 2. Reflux, 2 h	 R^1 R^2 H n-C_8H_{17} (89) n-C_4H_9 n-C_4H_9 (67)	218 378
	$TiCl_4$, Zn, THF, reflux, 6 h	 (68)	324
	1. $TiCl_4$, Zn, THF, reflux, 15 min 2. Reflux, 17 h	 (66)	216
	1. $TiCl_4$, Zn, THF, 1 h 2. Reflux, 4 h	 R 4-$MeOC_6H_4$ (45)  (34)	375
C_{14}			
	$TiCl_4$, Zn, py, THF, reflux, 20 min	 (52)	372
C_{15}			
	1. Pd/C, H_2, EtOH 2. $TiCl_4$, Mg/Hg, THF, rt, 12 h 3. H_2, Pd/C, EtOH	 (63)	379
	1. $TiCl_4$, Zn, CH_2Cl_2, rt, 30 min 2. rt	 (33)	202
	1. $TiCl_4$, Zn, THF, 0° 2. Reflux, 6 h	 (48)	380

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}			
	1. $TiCl_4$, Zn, THF, reflux 2. Reflux, 24 h 3. H_2, Pd/C, EtOH	 (67)[h]	368
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 20 h	 (53)	381
	$TiCl_4$, Zn, THF, –18°, 1 h; then reflux, 4 h	 (60)	382
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, overnight	 (quant)	383

C_{16}

	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 3 h	 (70)	197
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. THF/DMF, reflux, 16 h	 (41)	359

C_{17}

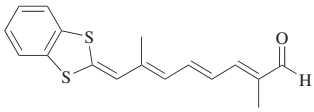
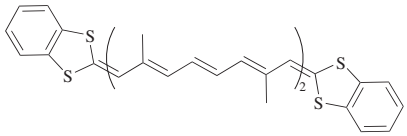
	1. $TiCl_4$, Zn/Cu, THF, reflux, 45 min 2. Reflux, 30 min; then addition of aldehyde; then reflux, 2 h	 (4)	384

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

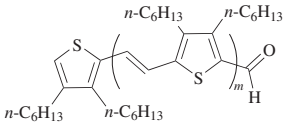
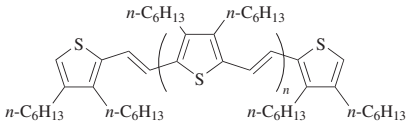
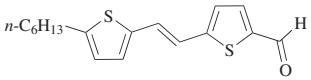
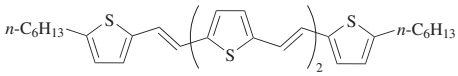
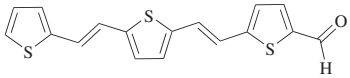
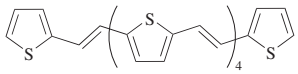
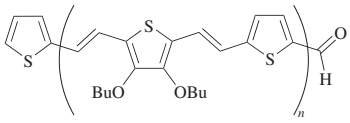
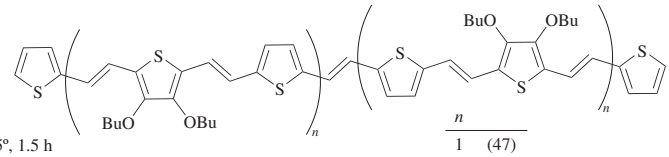
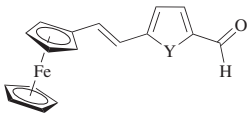
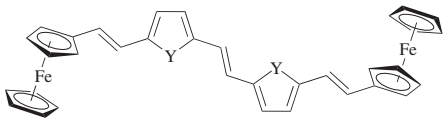
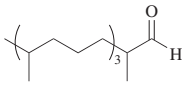
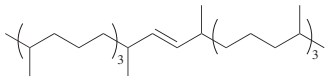
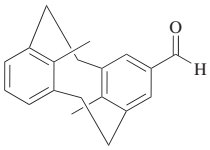
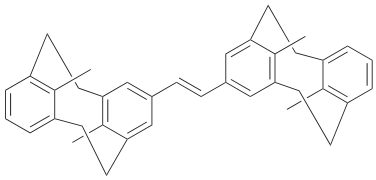
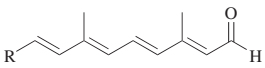
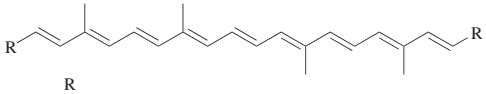
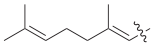
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17-35}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, time	 m n Time (h) 0 0 12 (74) 0 0 overnight (83) 1 2 12 (86) 1 2 overnight (70)	385, 384 387 385, 386 387
C_{17}			
	1. $TiCl_4$, Zn, THF 2. Reflux, 2 h	 (41)	218
	$TiCl_4$, Zn, dioxane, reflux, 2 h	 (40)	326
C_{17-29}			
	$TiCl_4$, Zn, THF, 65º, 1.5 h	 n 1 (47) 2 (37.5)	388
C_{17}			
	$TiCl_4$, Zn, THF, reflux, 3 h	 Y O (86) S (92)	389
C_{19}			
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 24 h	 (59)	390
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. rt	 (45)	391
C_{20}			
	1. $TiCl_3$, $LiAlH_4$, THF, rt, 2 h 2. rt, overnight	 R  (75) (84)	201

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

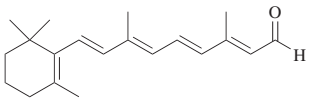
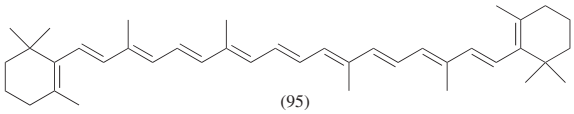
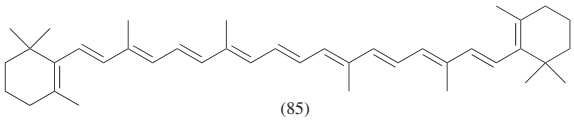
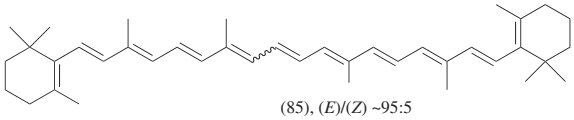
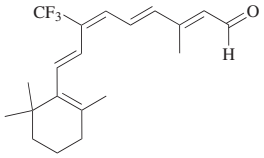
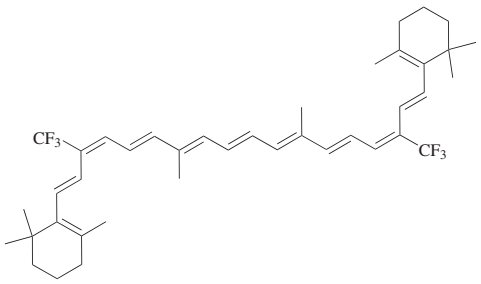
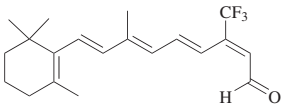
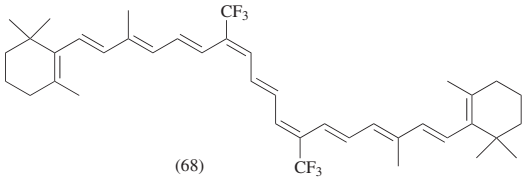
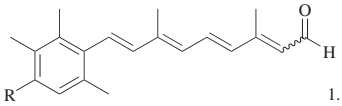
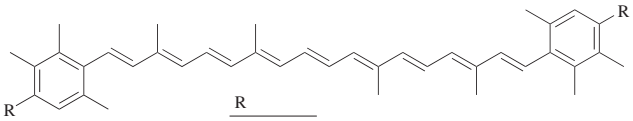
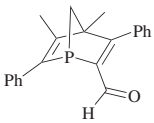
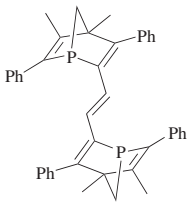
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 16 h	 (95)	27
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (85)	5
	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Reflux, 45 min	 (85), (*E*)/(*Z*) ~95:5	83
	$TiCl_4$, Zn, THF/CH_2Cl_2, 2 h	 (95)	122
	$TiCl_4$, Zn, THF/CH_2Cl_2, 2 h	 (68)	122
	1. $TiCl_3$, $LiAlH_4$, THF, rt, 2 h 2. rt, overnight	 R H (85) MeO (75)	203
C_{21}			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 1 h	 (50)	392

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

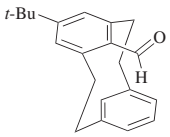
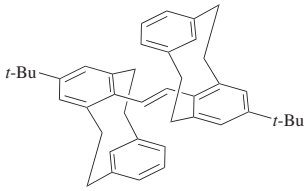
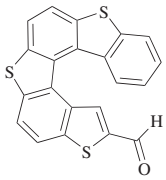
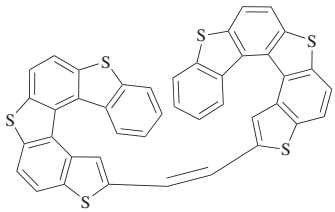
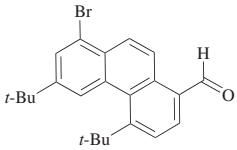
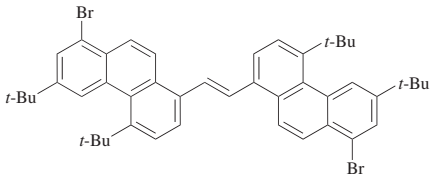
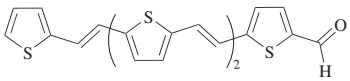
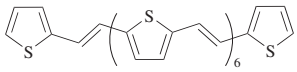
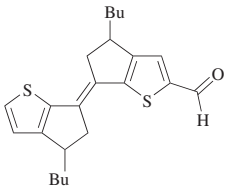
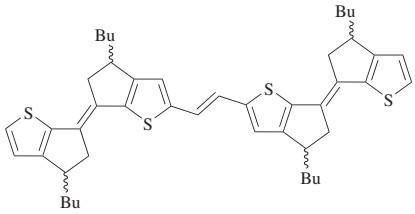
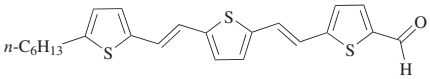
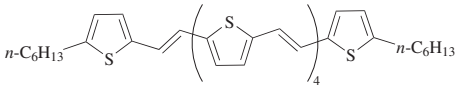
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2h 2. Reflux, 6 h	 (78)	374
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, overnight	 (quant)	383
C_{23}			
	1. $TiCl_4$, Zn, THF, 0° 2. Reflux, 8 h	 (78)	367
	$TiCl_4$, Zn, dioxane	 (5)	326
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 1.5 h	 (69)	393
	1. $TiCl_4$, Zn, THF 2. Reflux, 2 h	 (21)	218

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

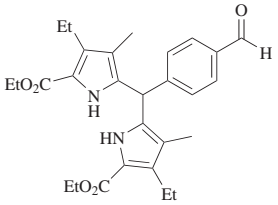
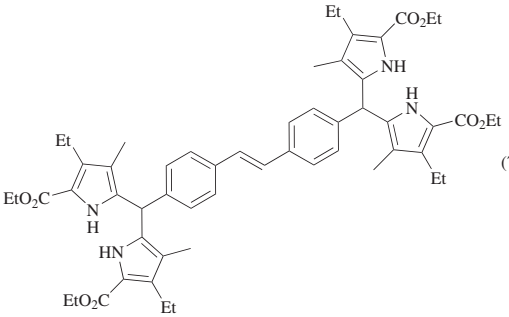
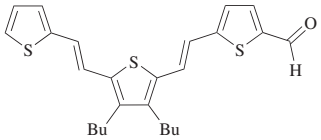
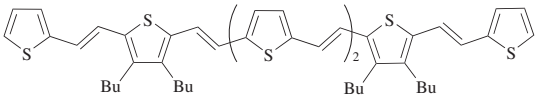
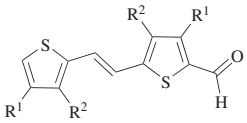
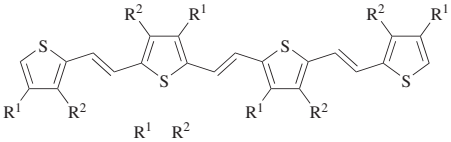
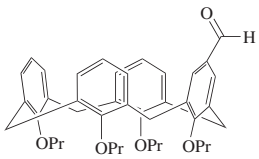
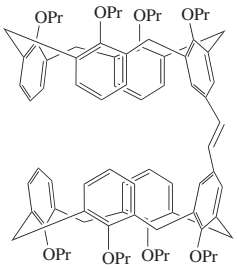
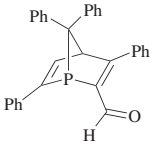
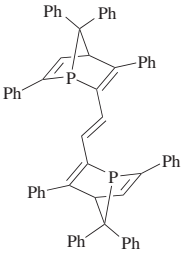
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 1 h	 (76)	394, 395
C_{25}			
	1. $TiCl_4$, Zn, THF 2. Reflux, 2 h	 (25)	218
C_{27}			
	1. $TiCl_4$, Zn, THF 2. Reflux, 2 h		
		R^1 R^2	
		H n-C_8H_{17} (71)	218
		Bu Bu (78)	378
C_{29}			
	1. $TiCl_3$, Zn, THF 2. Reflux, addition of aldehyde over 2 h; then reflux, 15 h	 (35)	241
C_{31}			
	$TiCl_4$, Zn, THF, rt	 (—)	392

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

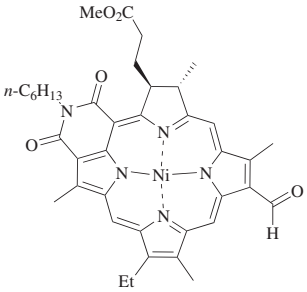
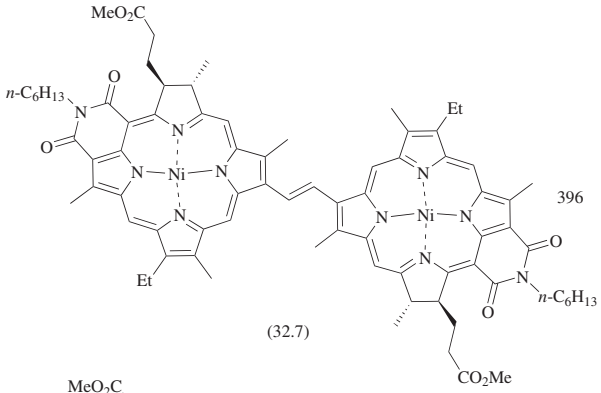
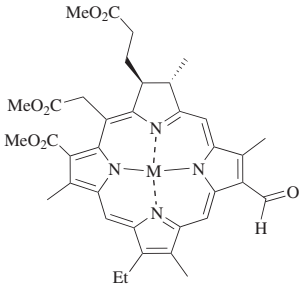
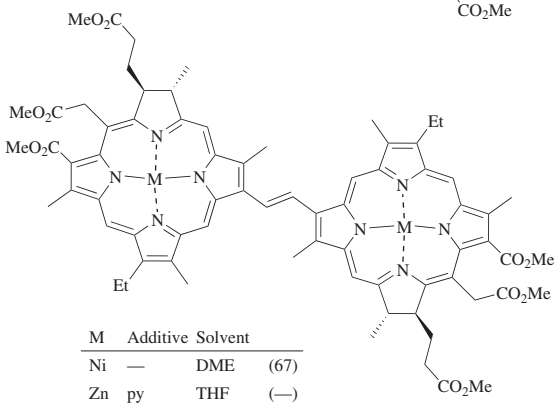
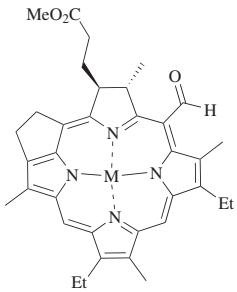
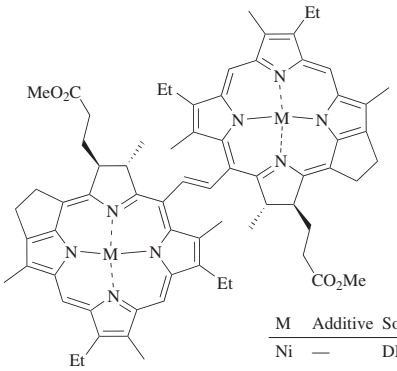
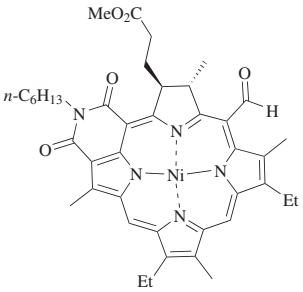
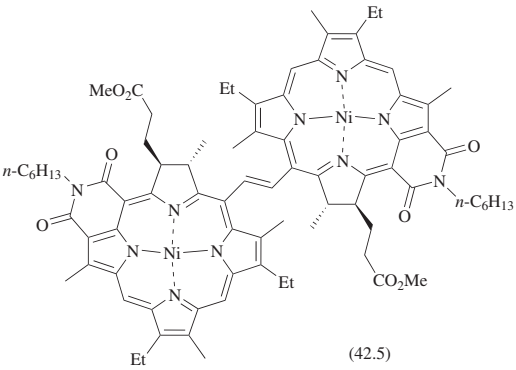
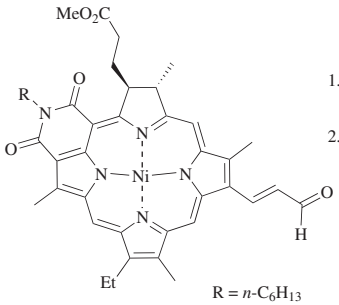
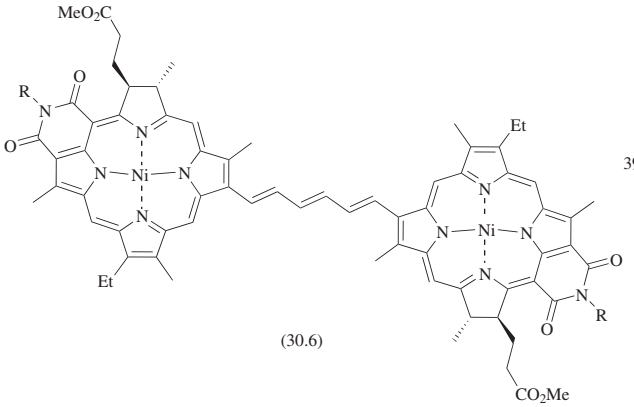
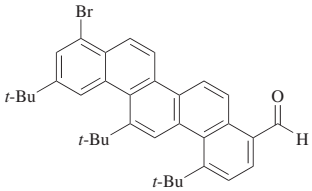
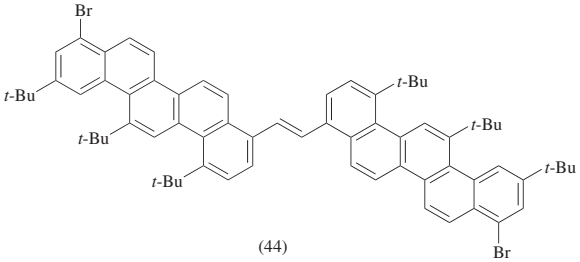
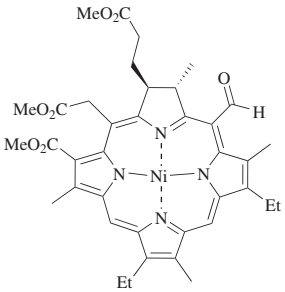
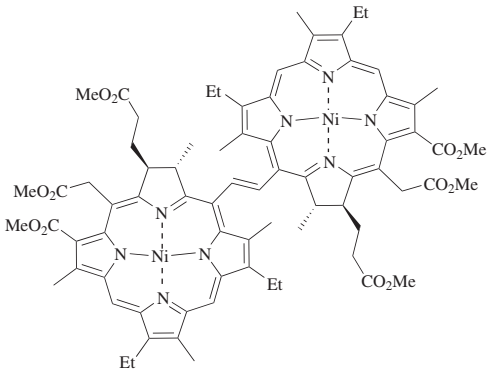
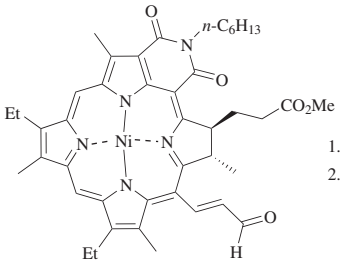
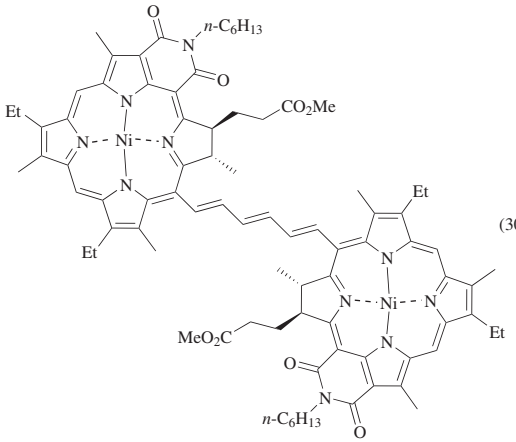
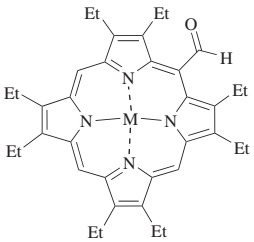
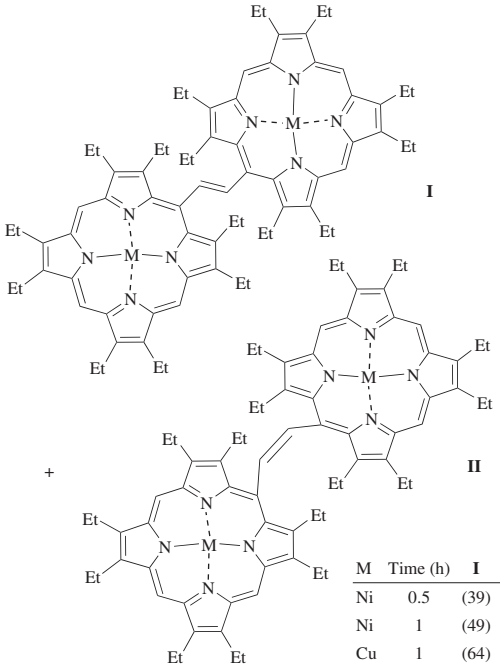
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{32} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 45 min	 (32.7)	396
C_{33} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, additive, solvent, reflux, 2 h 2. Reflux, 3 h	 M Additive Solvent Ni — DME (67) Zn py THF (—)	397
C_{34} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, additive, solvent, reflux, 2 h 2. Reflux, 3 h	 M Additive Solvent Ni — DME (72) Zn py THF (—)	397
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 45 min	 (42.5)	396

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{34}			
 R = *n*-C_6H_{13}	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 30–45 min	 (30.6)	396
C_{35}			
	1. $TiCl_4$, Zn, THF, 0° 2. Reflux, 8 h	 (44)	367
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 3 h	 (52)	397

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{36}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 45 min	 (30.6)	396

	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, time		

M	Time (h)	**I**	**II**	
Ni	0.5	(39)	(33)	214
Ni	1	(49)	(0)	215
Cu	1	(64)	(0)	215

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

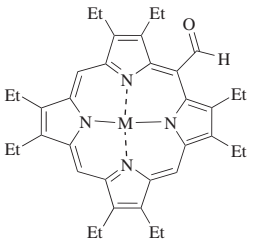
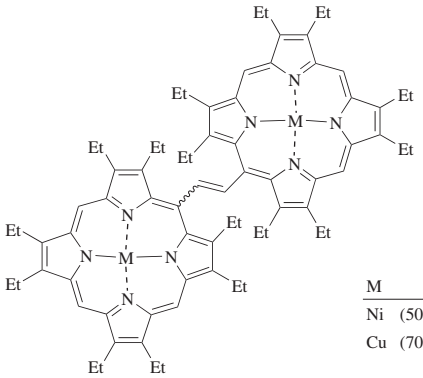
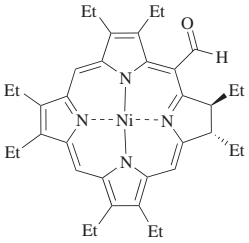
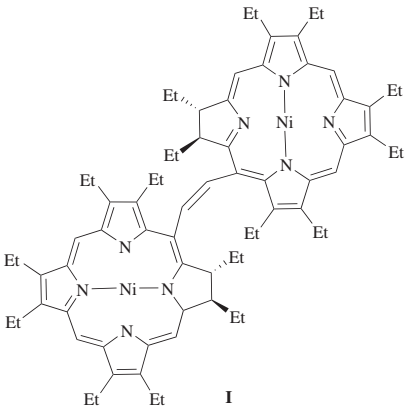
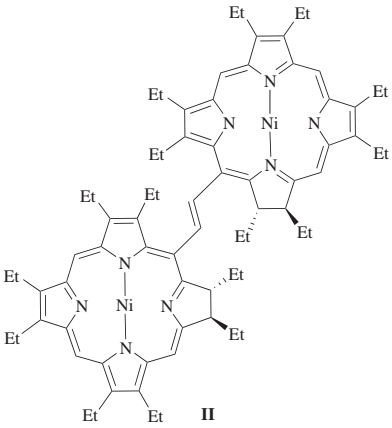
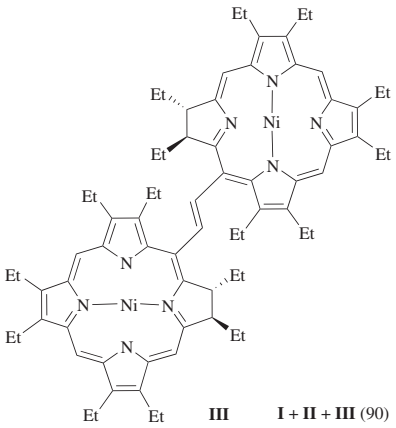
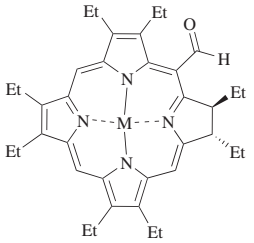
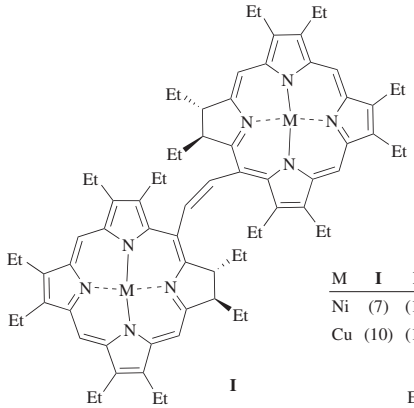
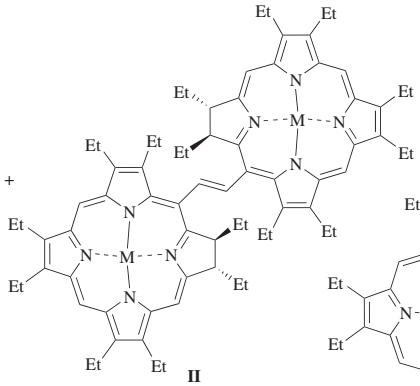
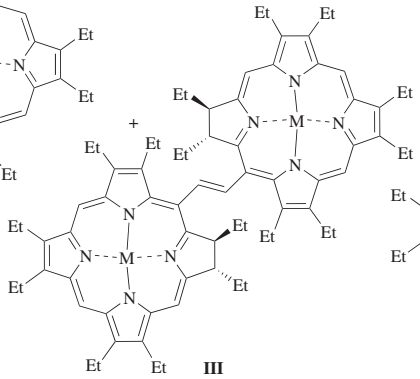
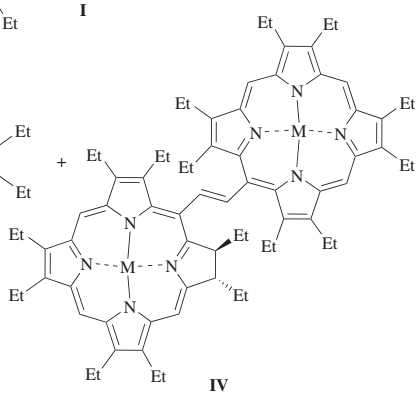
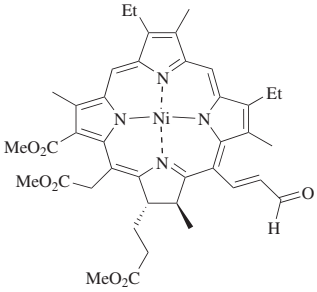
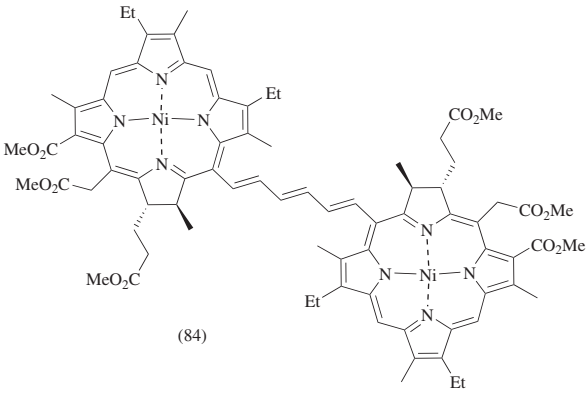
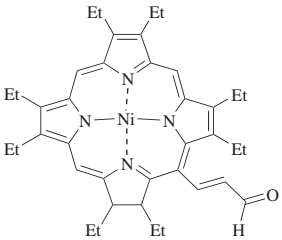
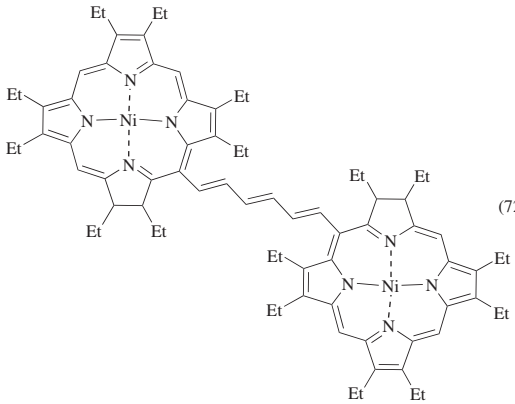
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{37}			
	—	 M (*E*)/(*Z*): Ni (50) —; Cu (70) 0:100	49
	"low-valent titanium-induced coupling"	 **I** +  **II** +  **III** **I** + **II** + **III** (90)	398

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{37}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 30 min	 **I** +  **II** +  **III** +  **IV** **M** **I** **II** **III** **IV** Ni (7) (11) (52) (11) Cu (10) (10) (8) (0)	50

	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 45 min	 (84)	215
C_{39}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 1 h	 (72)	215

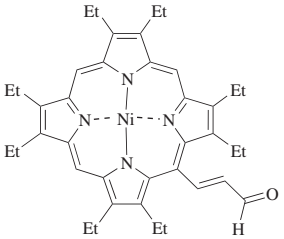
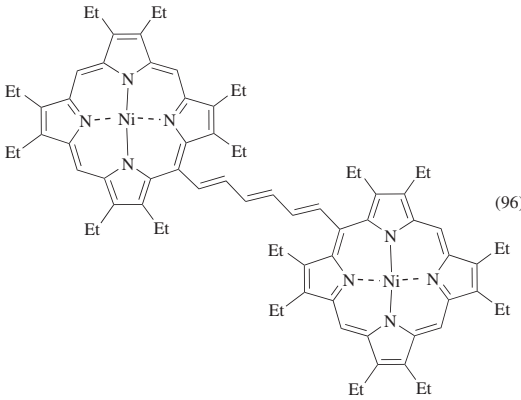
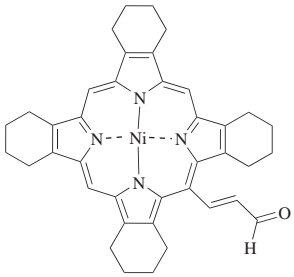
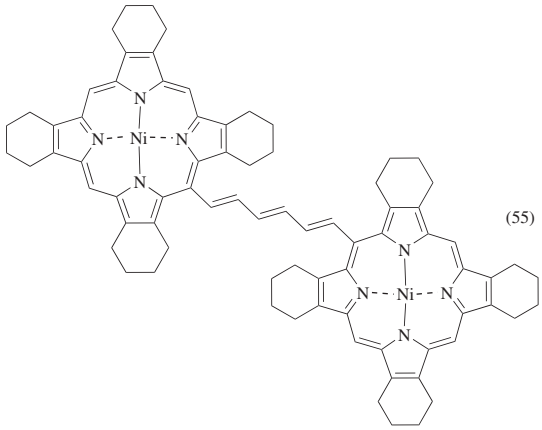
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{39}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 45 min	 (96)	215, 215a
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 1 h	 (55)	215

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

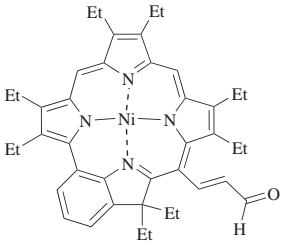
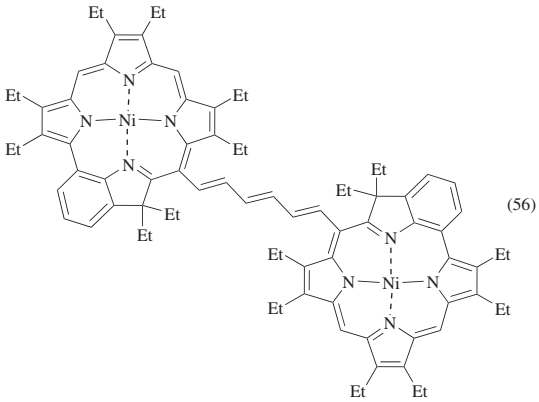
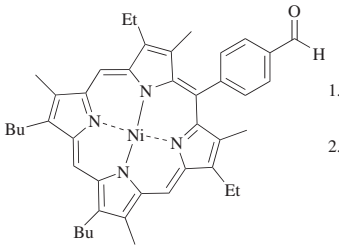
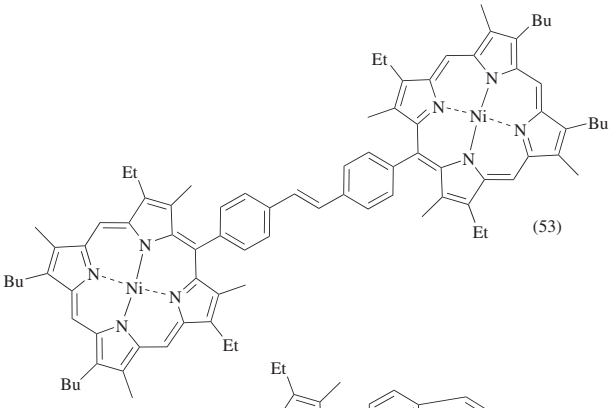
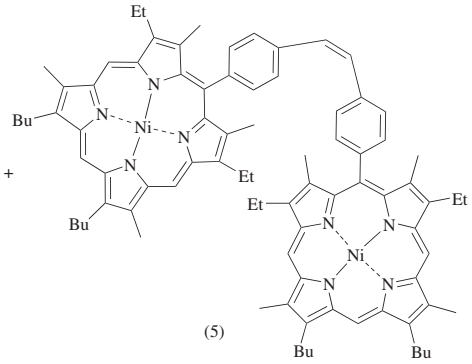
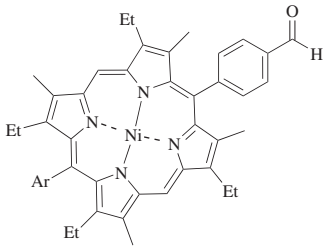
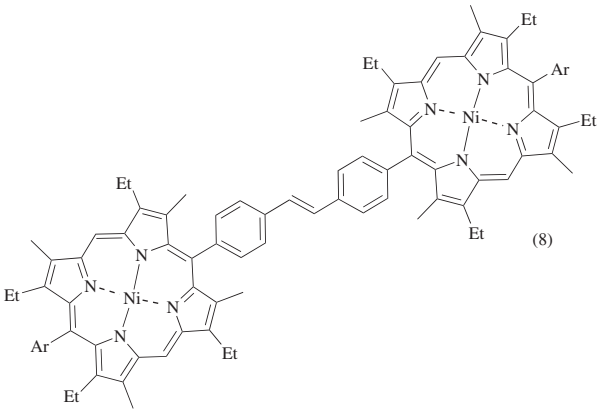
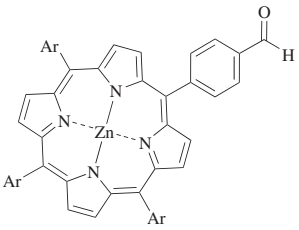
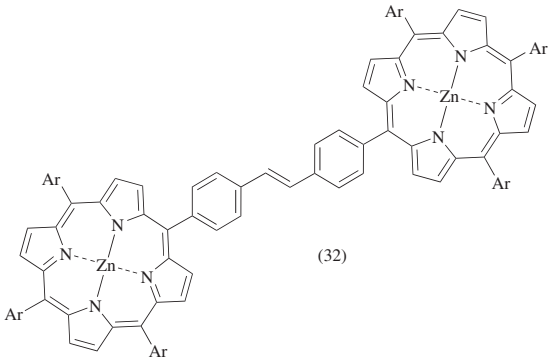
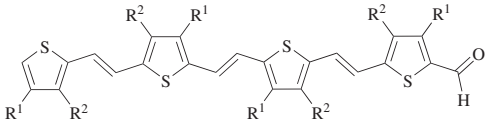
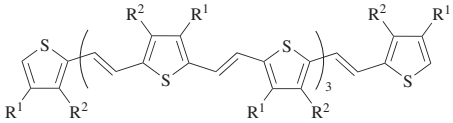
Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{42}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 1 h	 (56)	215
C_{43}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 3 h	 (53) +  (5)	394

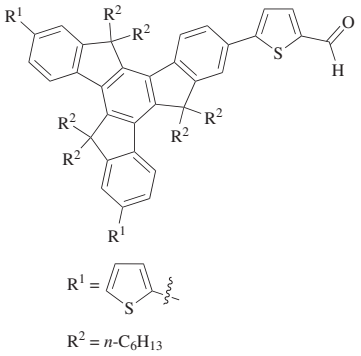
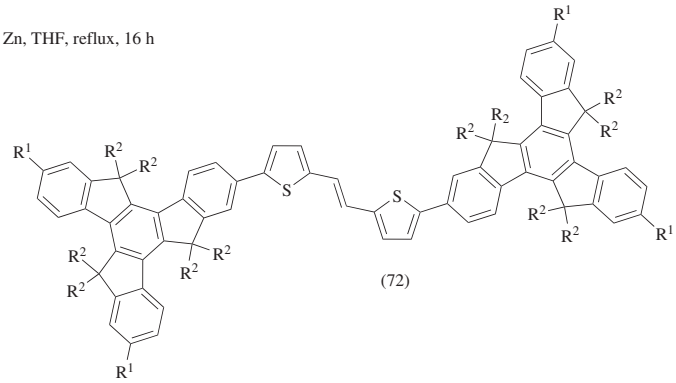
TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{45}			
 Ar = 2,5-$(MeO)_2C_6H_3$	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 3 h	 (8)	394

C_{48}			
 Ar = 4-MeC_6H_4	$TiCl_4$, Zn, THF, 0°	 (32)	399
C_{55}			
	1. $TiCl_4$, Zn, THF 2. Reflux, time		218

R^1	R^2	Time (h)	
H	n-C_8H_{17}	2	(25)
Bu	Bu	12	(52)

TABLE 1A. HOMOCOUPLING OF ALDEHYDES (*Continued*)

Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{76}			
	$TiCl_4$, Zn, THF, reflux, 16 h	 (72)	400

[a] The yield is after hydrogenation of the double bond.
[b] The Proton Sponge is *N,N,N,N*-tetramethyl-1,8-diaminonaphthalene.
[c] The electroreduction was carried out at V ≤ –1900 mV/SCE.
[d] The McMurry coupling product is an intermediate along the path to this product.
[e] [bmim]Cl($AlCl_3$) is 1-butyl-3-methylimidazolium chloroaluminate.
[f] The *Z*-isomer was isomerized to the *E*-isomer.
[g] The ratio of the *endo-endo* (*E*)-isomer to other isomers is given.
[h] Optically active starting material was employed.

TABLE 1B. HOMOCOUPLING OF KETONES

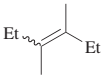
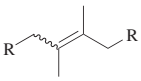
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3			
	1. $TiCl_3(THF)_3$, Mg, THF, 40°, 1 h 2. 40°, 1.5 h	(98)	4
C_{4-7}			
	$TiCl_4$, Zn	 R / (*E*)/(*Z*) Et (65) 1.1:1 Pr (61) 1.4:1 *i*-Pr (46) 1.5:1 *t*-$BuCH_2$ (48) 4:1	47
C_4			
	1. WCl_6, BuLi, THF, –78° to rt, 20 min 2. rt, 6 h	 (10)	2
C_{5-7}			
	1. $TiCl_4$, Zn, py, solvent, 0° 2. Reflux, 20 h	 R / Solvent / dr Et dioxane (61) ~1:3 *t*-Bu THF (48) 4:1	111
C_{5-15}			
	1. $TiCl_4$, Zn, py, THF, 0° 2. Reflux, 20 h	 R Et (62) Bn (80)	111

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

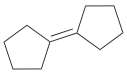
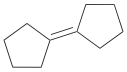
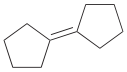
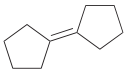
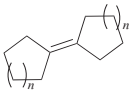
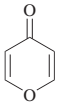
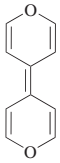
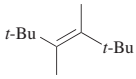
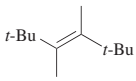
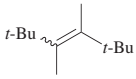
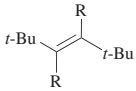
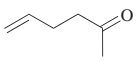
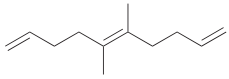
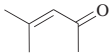
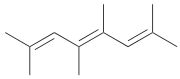
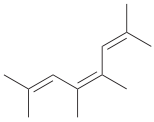
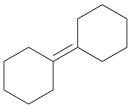
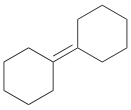
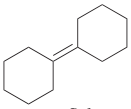
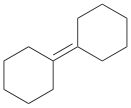
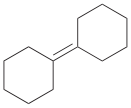
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5			
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 2 h	 (68)	114
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (40)	27, 62
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 10 h	 (83)	74
	$TiCl_4$, Hg/Mg, THF, 0°, 2 h; then reflux, 24 h	 (80)	331
C_{5-6}			
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2, 5 min 2. rt, time	 *n* Time (h) 1 6 (71) 2 5 (88)	115
C_5			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 4 h	 (69)	200
C_6			
	$TiCl_4$, Zn	 (62)	47
	$TiCl_3$, Zn, THF, reflux, 30 h	 (65)	181
	1. $TiCl_3$, $LiAlH_4$, THF, –78 to 0° 2. Reflux, 24 h	 (62), (*E*)/(*Z*) = 1:1	401
	$TiCl_3$, $LiAlH_4$	 R Me (—) CD_3 (—)	402
	$W_2(OCH_2CMe_3)_6(py)_2$, hexane, 22°, 2–24 h	 (21)	99, 100
	1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. Reflux, 10 h	 (60) +  (25)	129

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6			
	1. $TiCl_3$, M, solvent, reflux, time 2. Reflux, 16 h	 M Solvent Time Li DME 1 h (79) K THF 40 min (85)	27 27, 62
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 2 h	 (70)	114
	1. $TiCl_3$, C_8K, solvent, temp 1, time 1 2. Temp 2, time 2	 Solvent Temp 1 Time 1 (h) Temp 2 Time 2 (h) THF 70–75° 3 70–75° 12 (79) THF reflux 1.5 reflux 10 (83) DME reflux 2 reflux 12 (58)	72 73 84
	$TiCl_3$, Zn, DME, reflux, 21 h	 (57)	7
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 8 h	 (97)	6

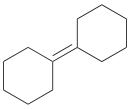
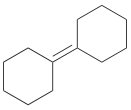
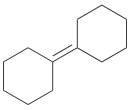
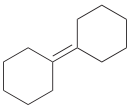
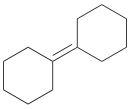
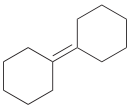
	1. $ZrCl_4$, Li, DME, rt, 1 h 2. Reflux, 10 h	 (43)	93
	1. $TiCl_4$, C_8K, THF, reflux, 1.5 h 2. Py, reflux, 10 h	 (75)	73
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5° 2. Microwave irradiation, 10 min	 (52)	121
	$TiCl_4$, Hg/Mg, THF, 0°, 2 h; then reflux, 24 h	 (70)	331
	$AlCl_3$, Zn, MeCN, reflux, 17 h	 (86)	88
	WCl_5, $LiAlH_4$, THF, rt, 6 h	 (55)	45

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

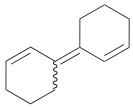
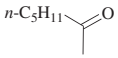
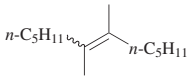
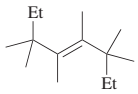
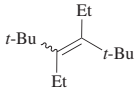
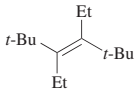
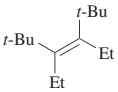
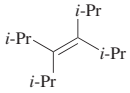
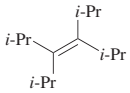
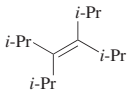
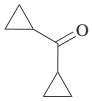
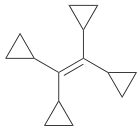
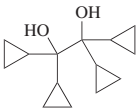
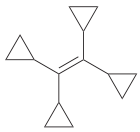
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6			
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 30 min	 (65), (*E*)/(*Z*) = 57:43	403
C_7			
	1. $NbCl_5$, $NaAlH_4$, THF/benzene, 0°, 10 min 2. Reflux, 3 h	 (33)	95
	$TiCl_4$, Zn	 (12)	47
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 45 h	 (47), (*E*)/(*Z*) = 12:1[a]	182
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 66 h	 (8.7) +  (0.4)	404
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2 2. rt, 8 h	(59)	115
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 8 h	 (59)	67
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (37)	27, 62
	$TiCl_3(DME)_{1.5}$, Zn/Cu	 (87)	6
	1. $TiCl_3/LiAlH_4$,[b] THF, 0°, 1.5 h 2. 0°, addition of ketone over 2 h; then 45°, 2 d	 (15) +  (7)	183
	1. $TiCl_4$, Zn, py, THF, 0° 2. Reflux, 20 h	 (25)	111

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

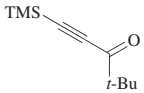
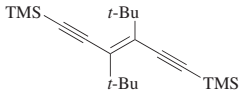
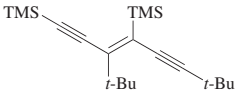
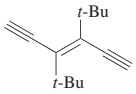
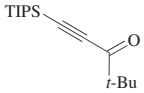
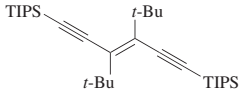
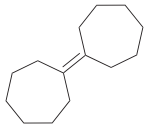
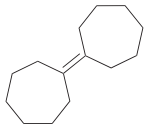
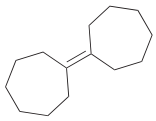
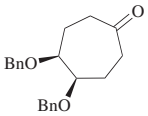
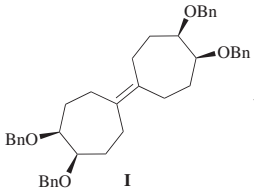
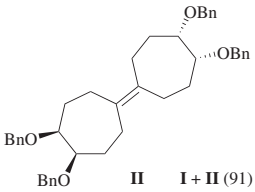
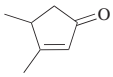
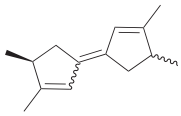
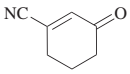
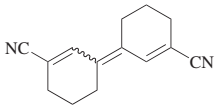
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	$TiCl_4$, Zn	 +  **I** **II** **I** + **II** (15–20), **I/II** = 2:1	405
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 10 h	 (15)	406
	$TiCl_4$, Zn, py, THF, 0°, 30 min; then rt, 2h	 (62)	405
	1. $TiCl_3$, M, solvent, reflux, time 2. Reflux, 16 h		27
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (95)	5
	1. $NbCl_5$, K, DME, 80°, 30 min 2. Reflux, 24 h	 (82)	96
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 48 h	 +  **I** **II** **I** + **II** (91)	407
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 14 h 2. rt, 3 h	 (93) dr 9:7	408
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 30 min	 (—)	409

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

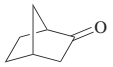
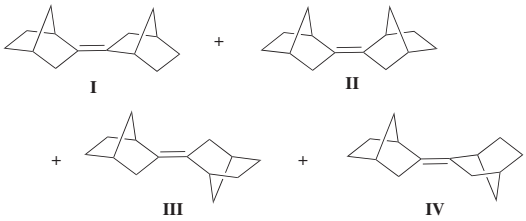
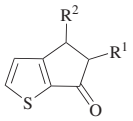
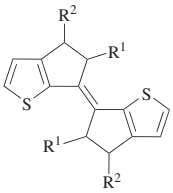
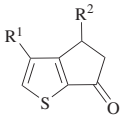
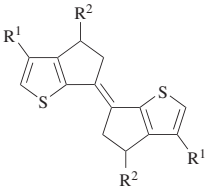
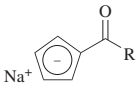
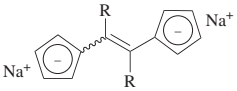
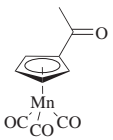
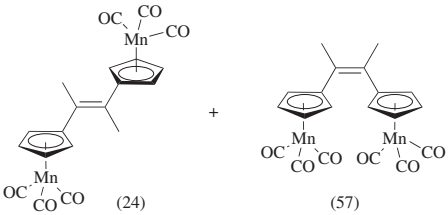
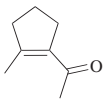
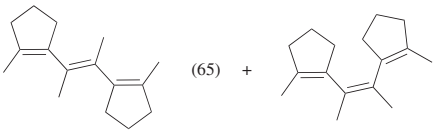
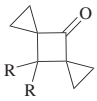
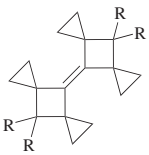
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_3$, Li, THF, reflux, 1 h 2. Reflux, 10 h	 **I** + **II** + **III** + **IV** (20)	410
C_{7-11}			
	1. $TiCl_4$, Zn, THF, reflux, 0.5 h 2. Reflux, 4 h	 R^1 R^2 H H (86) Me H (37) H Me (83) H Bu (50)	411
	$TiCl_4$, Zn, THF	 R^1 R^2 H H (—) H Bu (—)	393
C_{7-12}			
	1. $TiCl_3(THF)_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 12 h	 R Me (—) Ph (60)[d]	76
C_7			
	1. $TiCl_3$, C_8K, THF, reflux, 2.5 h 2. Reflux, 6 h	 (24) + (57)	77
C_8			
	1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. Reflux, 12 h	 (65) + (15)	129
C_{8-10}			
	1. $TiCl_3$, $LiAlH_4$, THF, 65°, 2 h 2. 55°, 2 d	 R R H H (22) $–(CH_2)_2–$ (28)	186

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

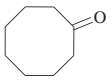
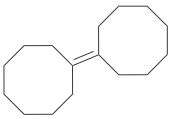
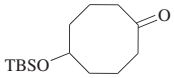
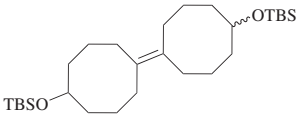
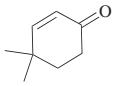
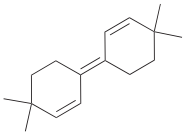
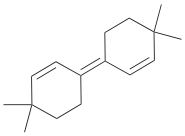
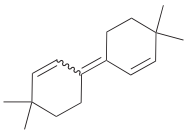
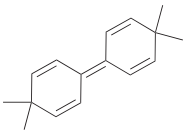
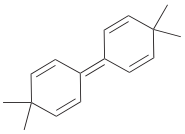
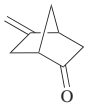
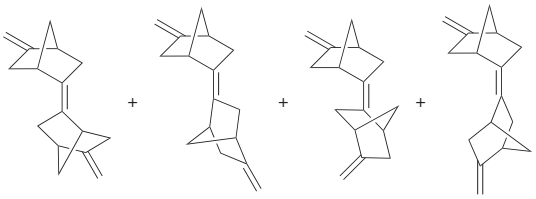
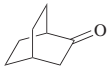
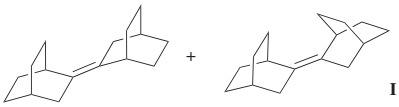
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (70)	27, 62
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 3 h	 (65) *syn*/*anti* ~1:1	412
	Zn, TMSCl, THF	 (23)	91
	Zn amalgam, $ClMe_2Si(CH_2)_2SiMe_2Cl$, THF, rt, overnight	 (76)	341
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 4 h	 (34)	200
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 4 h	 (97)	200
	Zn, HCl, THF, reflux, 10 h	 (—)	90
	1. $TiCl_4$, Zn, py, dioxane, reflux, 1 h 2. Reflux, 15 h	 **I** + **II** + **III** + **IV** (14) dr 1:1.2:1.3:1.2	413
	1. $TiCl_3$, Li, THF, reflux, 1 h 2. Reflux, 20 h	 **I** + **II** (25), **I**/**II** = 2:1	410

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

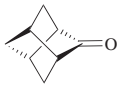
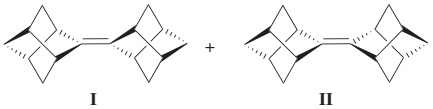
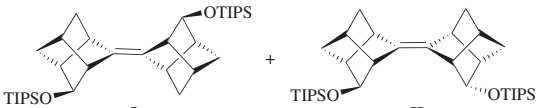
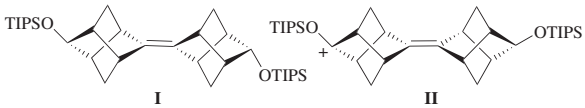
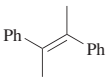
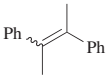
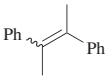
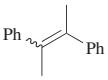
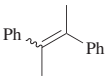
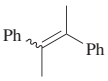
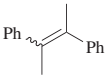
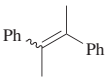
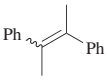
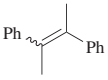
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	$TiCl_3(DME)_{1.5}$, Zn/Cu, DME, 40°, 19 h	 **I** + **II** (30)	194
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. 44°, 18 h	 **I** + **II** (40.1), **I/II** = 1:1	195
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. 40°, 19 h	 **I** + **II** (59)	195, 194
	$TiCl_2(THF)_2$, THF, reflux, 24 h	 (88)	34
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 16 h	 (94), (*E*)/(*Z*) = 90:10	27
	$TiCl_3$, Li, reflux, 16 h	 Solvent (*E*)/(*Z*) DME (92) 83:9 THF (89) 25:64	312
	1. $TiCl_3$, Li, THF, ultrasonication, 30°, 1 h 2. Ultrasonication, 30°, 45 min	 (87), (*E*)/(*Z*) = 21:66	312
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 2 h	 (82), (*E*)/(*Z*) = 85:15	114
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. Reflux, 1.5 h	 (89), (*E*)/(*Z*) = 56:44	67
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 10 h	 (86), (*E*)/(*Z*) = 20:1	73
	1. $TiCl_3$, C_8K, THF, 70–75°, 3 h 2. 70–75°, 12 h	 (84), (*E*)/(*Z*) = 2:1	72
	$TiCl_3(DME)_{1.5}$, Zn/Cu	 (—), (*E*)/(*Z*) = 8:92	414
	$TiCl_4$, Zn, additive, solvent reflux	 Additive Solvent Time (h) (*E*)/(*Z*) — dioxane 4 (92) 18:81 py THF 20 (87) 1:4	3 415

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

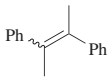
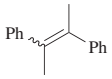
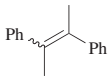
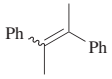
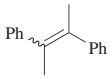
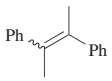
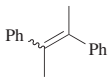
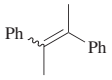
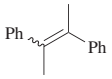
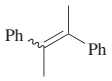
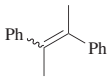
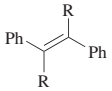
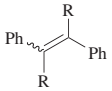
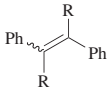
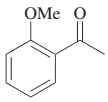
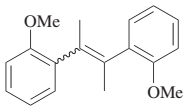
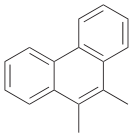
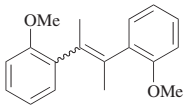
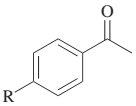
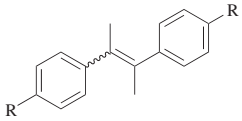
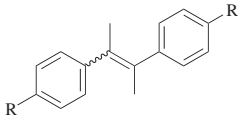
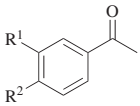
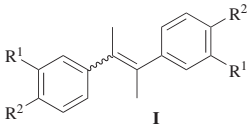
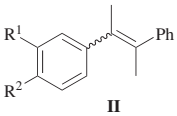
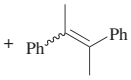
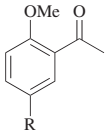
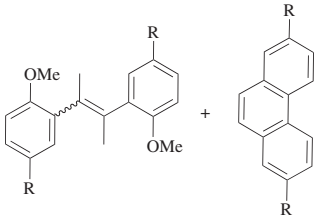
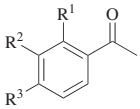
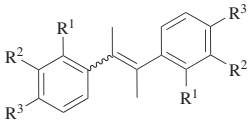
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5° 2. Microwave irradiation, 8 min	 (90), (*E*)/(*Z*) = 7:3	121
	$Ti(Oi\text{-}Pr)_4$, Mg, TMSCl, Et_3N, THF, 40°, 24 h	 (88), (*E*)/(*Z*) = 47:53	87
	$AlCl_3$, Zn, MeCN, reflux, 12 h	 (78), (*E*)/(*Z*) = 88:12	88
	1. $ZrCl_4$, Li, DME, rt, 1 h 2. Reflux, 6 h	 (92), (*E*)/(*Z*) = 81:11	93
	1. $NbCl_5$, $NaAlH_4$, THF/benzene, 0°, 10 min 2. Reflux, 2 h	 (73), (*E*)/(*Z*) = 1:9	95
	1. $NbCl_5$, MeLi, DME, 80°, 24 h 2. Reflux, 72 h	 (54), (*E*)/(*Z*) = 33:67	96
	$InCl_3$, Zn, MeCN, reflux, 9 h	 (60), (*E*)/(*Z*) = 80:20	104
	WCl_5, $LiAlH_4$, THF, rt, 6 h	 (33), (*E*)/(*Z*) = 20:13	45
	$W(CO)_6$, CH_2Cl_2, rt, 24 h	 (7), (*E*)/(*Z*) = 3:4	45
	WCl_6, electroreduction[e], THF, 4 h	 (46), (*E*)/(*Z*) = 30:16	103
	1. WCl_6, BuLi, THF, –78° to rt, 20 min 2. rt, 6 h	 (44), (*E*)/(*Z*) = 60:40	2
C_{8-13}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, time	 R Time (h) Me 10 (86) Ph 2 (87)	74
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2 2. Temp, time	 R Temp Time (h) (*E*)/(*Z*) Me 0–5° 8 (90) 80:20 $Cl(CH_2)_2$ 0–5° 5 (69) — Ph rt 5 (95) —	115
	1. $TiCl_3(THF)_3$, Mg, THF, 40°, 1 h 2. 40°, 1.5 h	 R (*E*) (*Z*) Me (—) (42) (29) Ph (67) (—) (—)	4

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	1. $TiCl_3$, Li, THF, reflux, 3 h 2. Py, reflux, 16 h	 (50) +  (41)	416
	$TiCl_n$, M		332
	1. $TiCl_3$, M, solvent, reflux, time 1 2. Reflux, time 2		
	[bmim]Cl($AlCl_3$),[f] Zn, rt, 30 min		46
	$TiCl_3$, Li	 **I** +  **II** +  **III**	332
C_{8-9}			
	1. $TiCl_3$, Li, reflux, 3 h 2. Additive, reflux, 16 h	 **I** + **II**	333
C_8			
	1. $TiCl_3$, Zn/Cu, solvent, reflux, 1 h 2. Reflux, 16 h		349

R^1	R^2	Solvent	**I**	**II**	**III**
MeO	H	THF	(53)	(18)	(10)
H	MeO	DME	(78)	(—)	(—)

R	Additive	**I**	**II**
H	Fullerene	(17)	(58)
H	—	(0)	(36)
Me	Fullerene	(12)	(49)
Me	—	(0)	(36)

n	M	Solvent	
3	Li	DME	(79)
3	Mg	THF	(85)
4	Zn	THF	(89)
4	Mg	THF	(90)

R	M	Solvent	Time 1 (h)	Time 2 (h)		(*E*)/(*Z*)	
HO	Zn	THF	3	6	(65)	35:65	346
Br	Li	DME	1	27	(67)	—	417
Br	$LiAlH_4$	THF	1	20	(51)	—	418

R		(*E*)/(*Z*)
H	(75)	3:97
MeO	(82)	15:85

R^1	R^2	R^3	Solvent	
H	AcO	H	DME	(75)
H	H	AcO	DME	(64)
TsO	H	H	THF	(64)

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

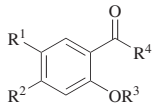
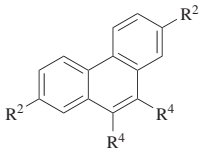
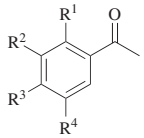
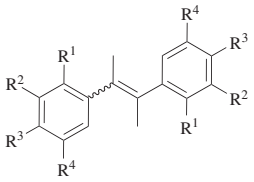
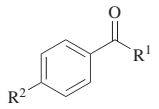
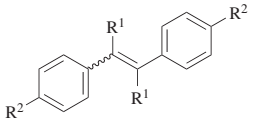
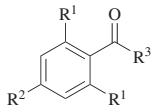
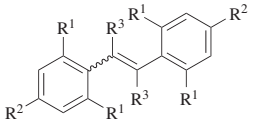
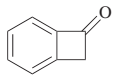
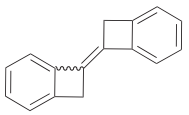
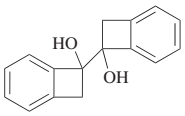
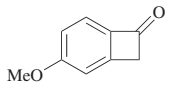
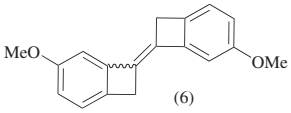
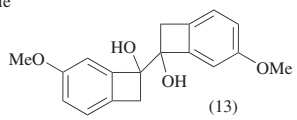
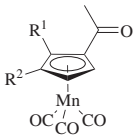
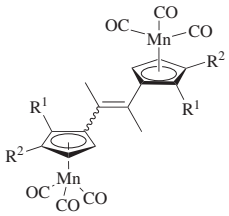
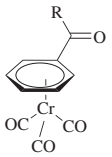
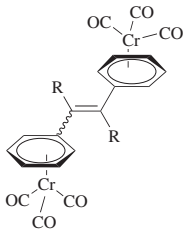
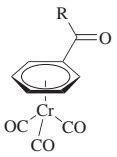
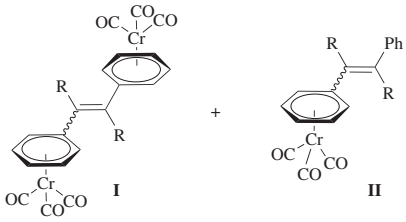
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{8-9}			
	$TiCl_3$, Li, THF, heat	 R^1 R^2 R^3 R^4 H H Me Me (36) H Me Me Me (38) H H Et Me (38) MeO H Me Me (32) H H Me Et (35)	332
C_8			
	$TiCl_4$, Zn, dioxane, reflux, 5 h	 R^1 R^2 R^3 R^4 AcO H H H (12) HO H H Br (13) H HO H H (55) H H HO H (62)	419
C_{8-13}			
	$TiCl_4$, Zn, py, THF, reflux, 20 h	 R^1 R^2 $(E)/(Z)$ Me H (81) 26:74 Me MeO (50) 16:84 Et H (59) 27:73 Et HO (35) 22:78 Et MeO (44) 25:75 Pr H (55) 11:89 *i*-Pr H (25) 88:12 *t*-Bu H (3) 100:0 $4\text{-}MeOC_6H_4$ MeO (45) —	48
C_{8-16}			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 8 h	 R^1 R^2 R^3 $(E)/(Z)$ H H Me (70) 1:4.5 MeO MeO Me (42) 1:1.8 Me Me Me (22.5) 1:1.2 H Me Ph (70) 1:1 Me Me Ph (18) 1:0.45	420
C_8			
	1. $TiCl_4$, Zn, THF 2. Reflux, 21 h	 (22), $(E)/(Z)$ = 1:1 +  (—)	187, 421
	$TiCl_4$, Zn, THF, reflux, 15 h	 (6) +  (13)	188

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 2.5 h 2. Reflux, 4 h	 R^1 R^2 Me H (44)[c] H Me (59)[c]	77
C_{8-11}			
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 4 h	 (*E*)/(*Z*) ~3:1 R Me (80) Et (85) Pr (75) Bu (79)	422
C_{8-13}			
	$NbCl_3$, THF, rt, 24 h	 **I** + **II** R **I** (*E*)/(*Z*) **II** (*E*)/(*Z*) Me (39) 7:3 (37) 2:1 Ph (38) (—) (48) (—)	97

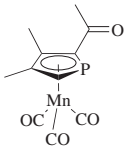
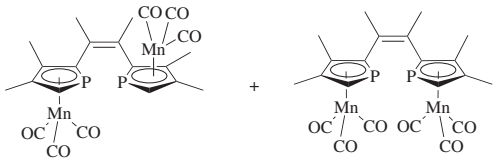
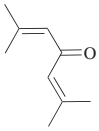
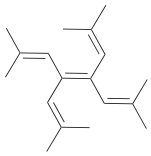
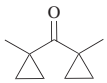
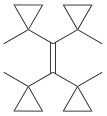
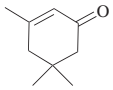
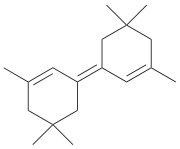
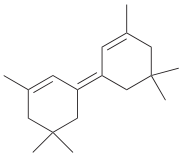
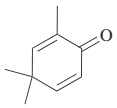
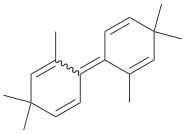
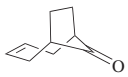
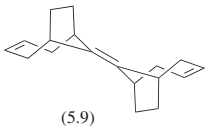
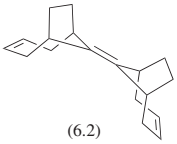
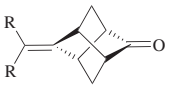
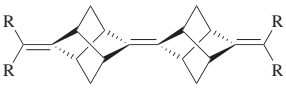
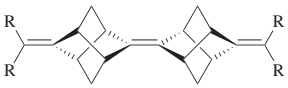
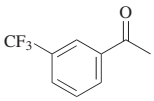
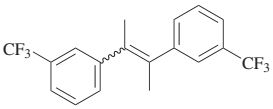
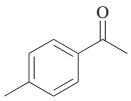
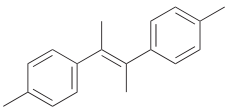
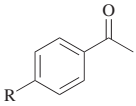
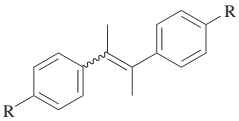
C_8			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 18 h	 (45) + (27)	208
C_9			
	1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. *t*-BuOH, reflux, 10 h	 (60)	129

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9			
	1. $TiCl_3/LiAlH_4$,[b] $LiAlH_4$, THF, reflux, 1 h 2. 50°, 2 d	 (13)	184
	1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. *t*-BuOH, reflux, 3 h	 (40) +  (35)	129
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 4 h	 (73) dr 1:3	200
	1. $TiCl_3$, K, DME, reflux, 1 h 2. Reflux, 16 h	 (5.9) +  (6.2)	423
C_{9-11}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, time 1 2. Temp, time 2	 **I** +  **II**	

R	Time 1 (h)	Temp (°)	Time 2 (h)	**I + II**	**I/II**	Refs.
H	6	40	19	(12)	98:2	195, 194
Me	3	45–50	16.5	(1.3)	98:2	195

C_9			
	1. $TiCl_3$, Li, DME, reflux, 1 h 2. Reflux, 27 h	 (60)	417
	$W_2(OCH_2CMe_3)_6(Py)_2$, hexane, 22°, 2–24 h	 (51)	99, 100
C_{9-12}			
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, time		

R	Time (h)		(*E*)/(*Z*)	Refs.
Me	2.5	(72)	78:22	67
t-Bu	3	(64)	76:24	

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

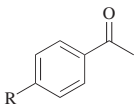
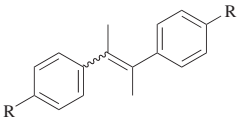
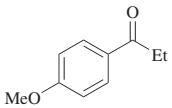
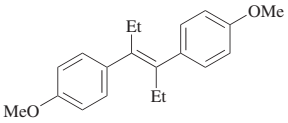
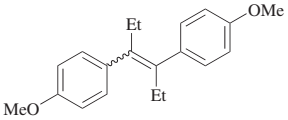
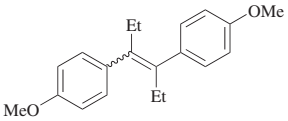
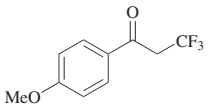
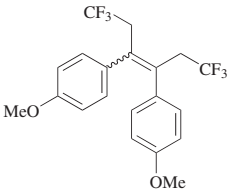
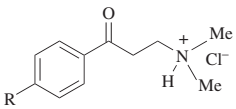
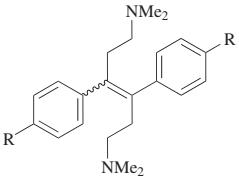
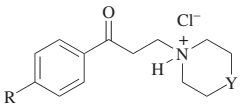
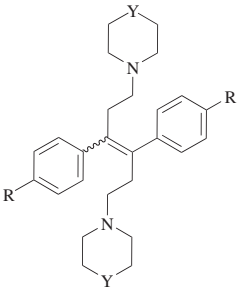
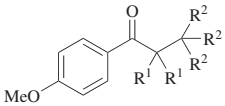
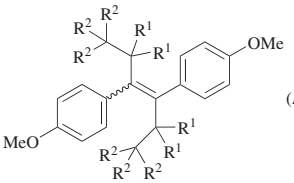
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{9-12}			
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, time	 R Time (h) (*E*)/(*Z*) Me 3 (82) 65:35 *t*-Bu 10 (78) 75:25	114
C_9			
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (85)	5
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 21 h	 (73), (*E*)/(*Z*) = 5:95	424
	$InCl_3$, Zn, MeCN, reflux, 14 h	 (80), (*E*)/(*Z*) = 95:5	104
	$TiCl_3$, Zn/Cu, THF	 (75), (*E*)/(*Z*) = 1:4	425
C_{9-10}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 2 d 3. 10% aq K_2CO_3	 R H (71) Br (45) Me (38)	426
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 2 d 3. 10% aq K_2CO_3	 R Y H CH_2 (81) Br CH_2 (51) MeO CH_2 (33) Me CH_2 (66) H O (57)	426
C_9			
	1. $TiCl_3$, Li, DME, reflux, 3 h 2. Reflux, 16 h	 (*E*)/(*Z*) = 5:95 R^1 R^2 D H (58) H D (—)	427

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

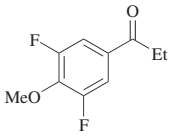
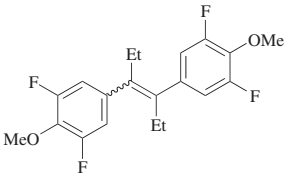
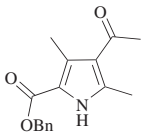
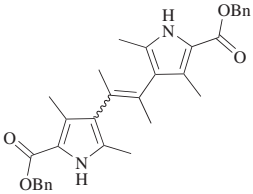
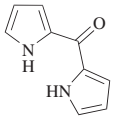
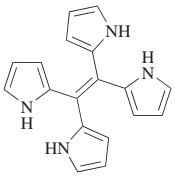
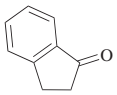
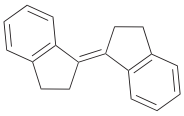
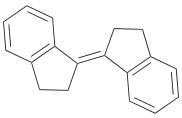
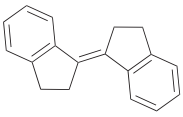
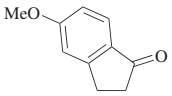
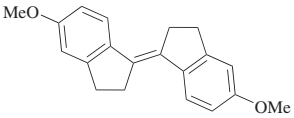
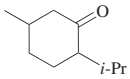
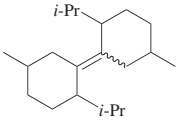
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9			
	1. $TiCl_3$, Zn/Cu, THF, reflux, 1 h 2. Reflux, addition of ketone over 1 h; then reflux, 16 h	 (96)	428
	$TiCl_4$, Zn, THF	 (—)	211
	—	 (56)	429
	1. $TiCl_4$, Zn, THF 2. Reflux, 16 h	 (69)	430
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5° 2. Microwave irradiation, 5 min	 (74)	121
	—	 (70–80)	431
	1. $TiCl_4$, Zn, 0°, 10 min 2. Reflux, 20 h	 (53)	432
C_{10}			
	1. $TiCl_4$, Zn, py, THF, 0° 2. Reflux, 20 h	 (51) dr 3:1	111

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

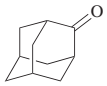
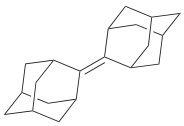
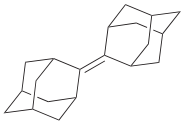
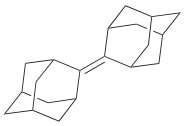
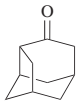
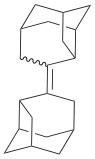
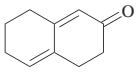
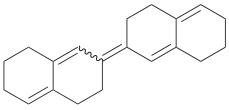
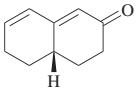
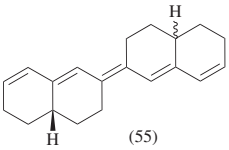
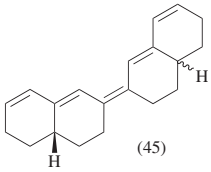
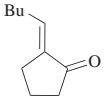
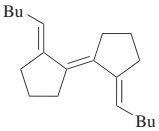
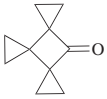
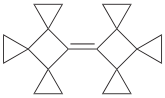
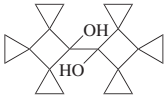
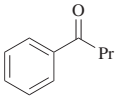
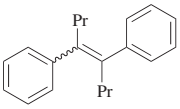
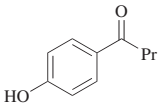
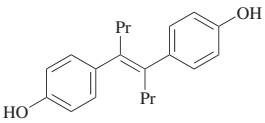
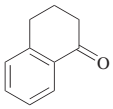
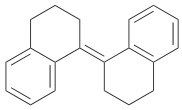
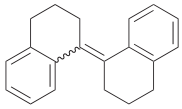
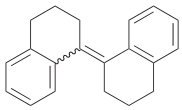
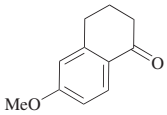
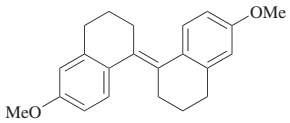
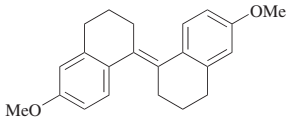
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	1. $TiCl_3$, M, solvent, reflux, time 2. Reflux, 16 h	 M Solvent Time Li DME 1 h (82) K THF 40 min (91)	27 27, 62
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (85)	5
	$TiCl_4$, Zn, py, THF, reflux, 46 h	 (98.2)	433
	1. $TiCl_4$, Zn, py, THF, 0° 2. Reflux, 18 h	 (45)	111
	1. $TiCl_4$, Zn, py, THF 2. rt, 15 min	 (54), (*E*)/(*Z*) = 82:18	434
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 5 min	 (55) +  (45)	403
	Zn amalgam, $ClMe_2Si(CH_2)_2SiMe_2Cl$, THF, rt, overnight	 (72)	341
	$TiCl_3$, $LiAlH_4$, THF, rt, 3 d	 (8) +  (—)	435
	$TiCl_4$, Zn, THF, 110°, microwave irradiation, 10 min	 (93), (*E*)/(*Z*) = 9:1	317
	$TiCl_3$, $LiAlH_4$, THF	 (42)	436

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5° 2. Microwave irradiation, 5 min	 (89)	121
	1. $TiCl_4$, Zn, 0°, 10 min 2. Reflux, 20 h	 (53), (*E*)/(*Z*) = 7:3	432
	$AlCl_3$, Zn, MeCN, reflux, 18 h	 (88), (*E*)/(*Z*) = 99:1	88
	$AlCl_3$, Zn, MeCN, reflux, 12 h	 (85)	88
	1. $TiCl_4$, Zn, THF 2. Reflux, 20 h	 (41)	187

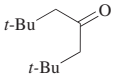
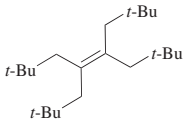
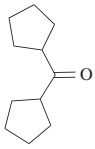
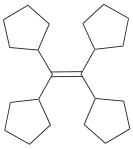
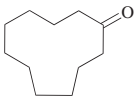
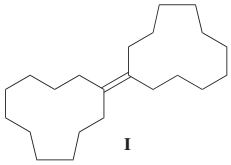
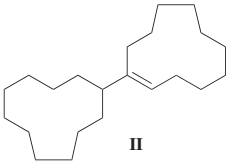
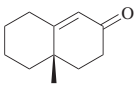
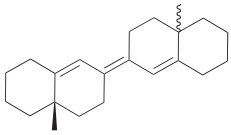
C_{11}			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 8 h	 (38)	437
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt, 8 h	 (72)	67
	$TiCl_4$, Zn, dioxane, –10° to reflux, 21 h	 +  **I** **II** **I** + **II** (100), **I**/**II** = 88:12	438
	Zn, TMSCl, THF	 (85)	91

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

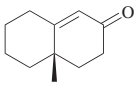
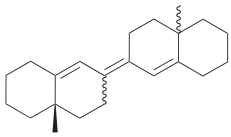
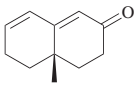
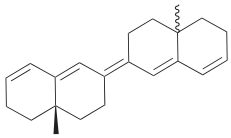
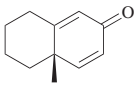
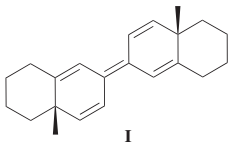
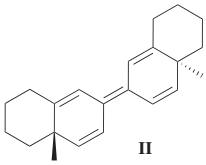
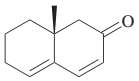
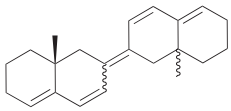
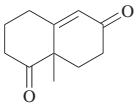
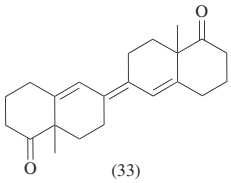
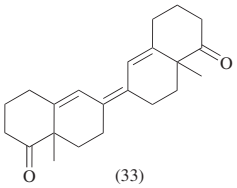
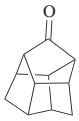
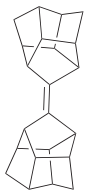
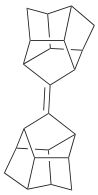
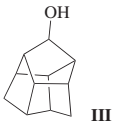
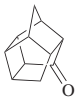
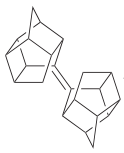
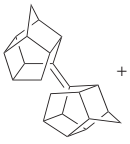
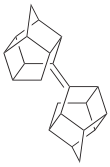
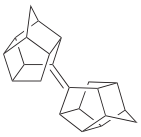
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	1. $TiCl_4$, Zn, py, THF 2. —	 (39) dr 20:15:42:23[g]	439
	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. rt, 1 h	 (80)	439
	1. $TiCl_4$, Zn, py, THF, 0° 2. 0°, 30 min	 **I** +  **II** **I** + **II** (91), **I/II** = 50:50	440
	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. rt, 1 h	 (38)	439
	1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. 20°, 12 h	 (33) +  (33)	129
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, 24 h	 **I** +  **II** +  **III** **I** + **II** (60), **III** (25)	190
	$TiCl_4$, Zn, py, THF, reflux, 3 d	 +  +  +  **I** **II** **III** **IV** **I** + **II** + **III** + **IV** (44)	193

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

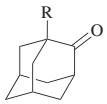
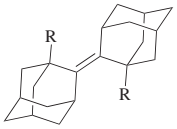
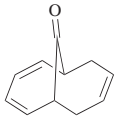
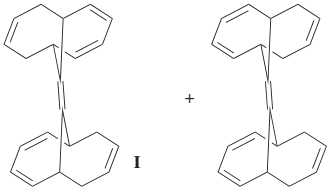
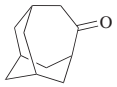
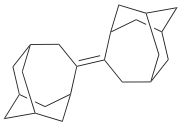
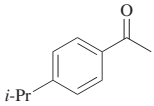
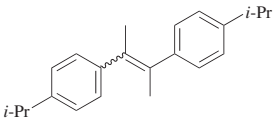
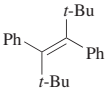
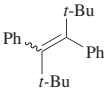
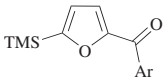
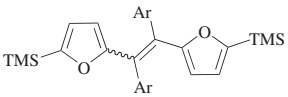
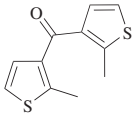
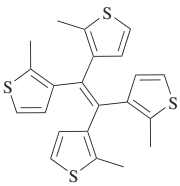
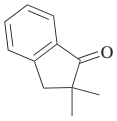
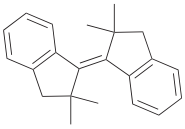
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11-12}			
	$TiCl_3$, K	 R: Me (52), Et (40)	47
C_{11}			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 4 h	 **I** + **II** (3.1)	441, 442
	1. $TiCl_3$, $LiAlH_4$, THF, 30 min 2. Reflux, 8 h	 (40)	443
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 10 h	 (75), (*E*)/(*Z*) = 80:20	114
	$TiCl_4$, Zn	 (48)	47
	$AlCl_3$, Zn, MeCN, reflux, 11 h	 (82), (*E*)/(*Z*) = 90:10	88
 Ar = 4-$MeOC_6H_4$	1. $TiCl_4$, Zn, THF, reflux, 3 h 2. Reflux, 40 min	 (72), (*E*)/(*Z*) = 3:1	444
	$TiCl_4$, Zn, py, THF	 (59)	445
	$TiCl_4$, Zn, THF, reflux	 (52)	446

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

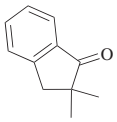
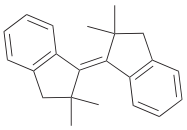
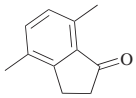
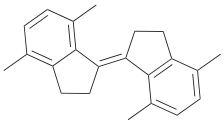
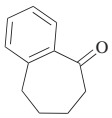
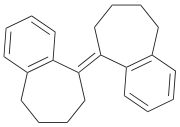
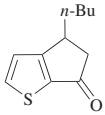
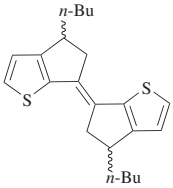
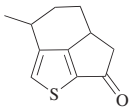
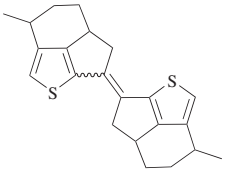
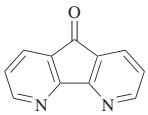
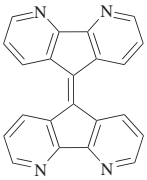
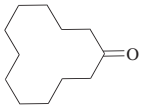
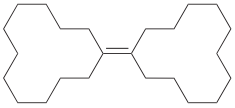
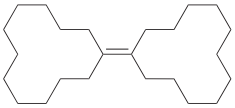
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	1. $TiCl_4$, Zn, THF 2. Reflux, 16 h	 (42)	430
	1. $TiCl_4$, Zn, 0°, 10 min 2. Reflux, 18 h	 (95)	432
	1. $TiCl_4$, Zn, THF 2. Reflux, 22 h	 (27)	187
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 4 h	 (50)	411
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 4 h	 (38)	447
	$TiCl_3$, $LiAlH_4$, THF, reflux, 12 h	 (20)	213
C_{12}			
	1. $TiCl_3$, M, solvent, reflux, time 2. Reflux, 16 h		
		M Solvent Time (h) Li DME 1 (65) K THF 0.75 (90)	27 27, 62
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 12 h	 (85)	84

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

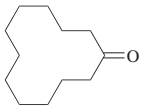
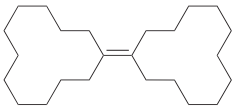
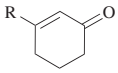
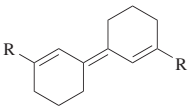
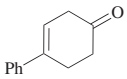
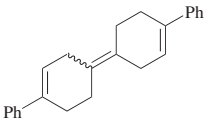
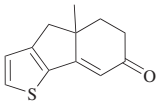
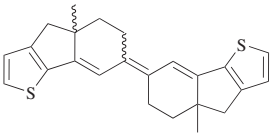
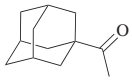
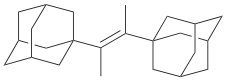
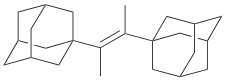
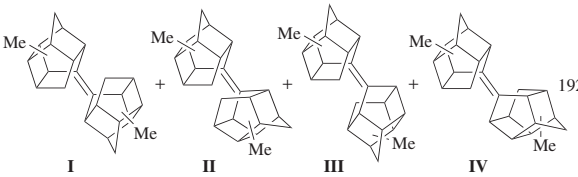
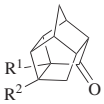
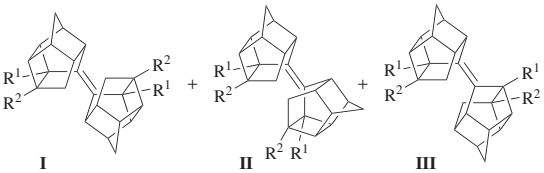
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}			
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (80)	5
C_{12-16}			
	$TiCl_4$, Zn, dioxane	 R: Ph (—); 2-Np (—)	448
C_{12}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 2.5 h 2. Reflux, 12 h	 (31) dr 43:54	449
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 30 min	 (84)	450, 451
	$TiCl_4$, Zn	 (15)	47
	1. $TiCl_4$, Zn, py, THF, 0° 2. Reflux, 3 d	 (15)	111
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, 24 h	 **I** + **II** + **III** + **IV** (73)	192
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, 24 h	 **I** + **II** + **III** + **IV** R^1 R^2 **I + II + III + IV** H Me (50) Me H (62)	192

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

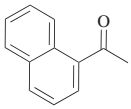
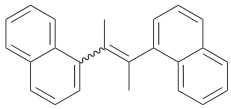
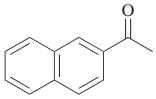
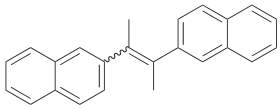
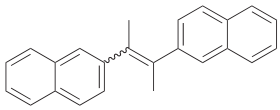
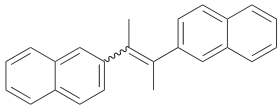
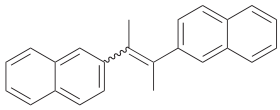
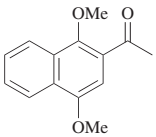
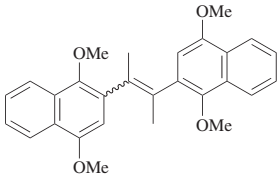
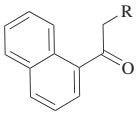
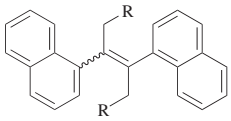
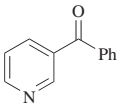
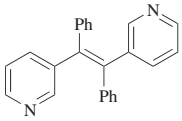
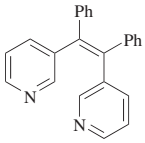
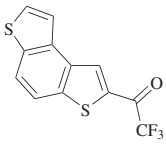
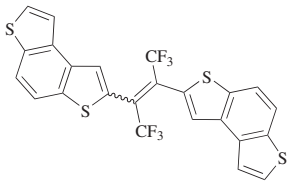
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}			
	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 1 h	 (88), (*E*)/(*Z*) = 82:18	69
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. Reflux, 4.5 h	 (68), (*E*)/(*Z*) = 60:40	67
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 6 h	 (68), (*E*)/(*Z*) = 72:28	114
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2, 5 min 2. 0–5°, 6 h	 (93), (*E*)/(*Z*) = 64:36	115
	$TiCl_4$, Zn, THF	 (—), (*E*)/(*Z*) = 20:80	140
	1. $TiCl_3$, $LiALH_4$, THF, rt 2. Reflux, 3 h	 (41.3)	452
C_{12-22}			
	$TiCl_4$, $LiAlH_4$	 R: H (—); Me (—); *n*-C_6H_{13} (—); *n*-$C_{10}H_{21}$ (—)	453
C_{12}			
	$TiCl_3$, $LiAlH_4$, THF, reflux, 12 h	 (13) +  (18)	213
	1. $TiCl_4$, Zn, py, THF, reflux, 2.25 h 2. Reflux, 13.75 h	 (16), (*E*)/(*Z*) = 65:35	217

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

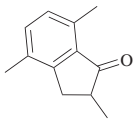
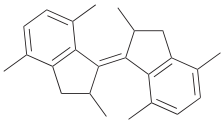
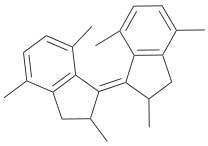
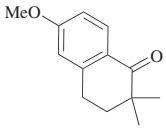
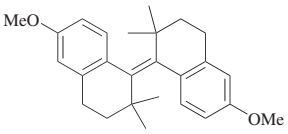
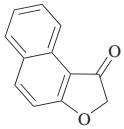
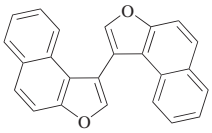
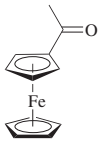
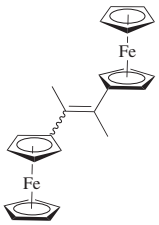
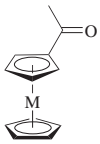
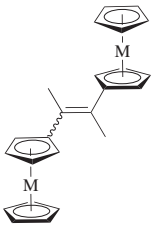
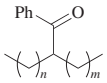
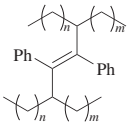
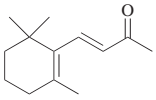
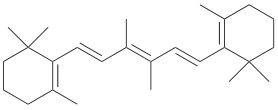
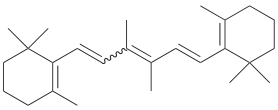
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 d	 (7) +  (25)	454
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 15 min 2. Reflux, 52 h	 (18)	187
	1. $TiCl_4$, Zn, DME, reflux 2. Reflux, 18 h 3. DDQ, benzene, reflux, 4 h	 (78)	455
	$TiCl_4$, Zn	 (69), (*E*)/(*Z*) = 3:1	47
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 3 h 2. Reflux, time		
		M Time (h) (*E*)/(*Z*) Fe 3 (54) — Ru 5 (43) 1.3:1	456 457
C_{12-20}			
	$TiCl_4$, Zn, THF, reflux, 48 h		458
		m *n* 2 2 (12–80) 3 3 (12–80) 3 5 (12–80) 5 5 (39)	
C_{13}			
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 20 min 2. Tertiary amine, reflux, 3 h		
		Tertiary amine Bu_3N (91) Proton Sponge[h] (94)	110
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (53), (*E*)/(*Z*) = 5:4	361

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

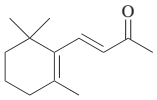
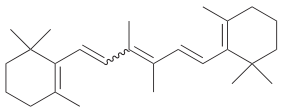
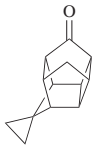
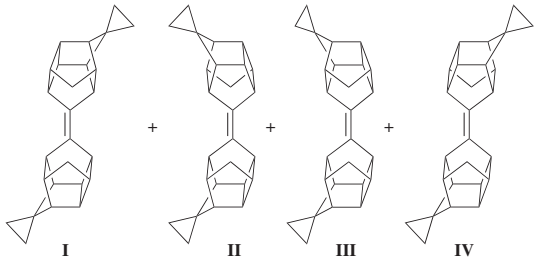
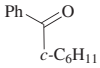
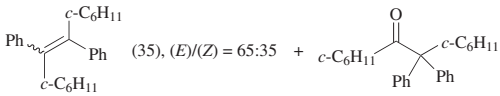
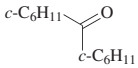
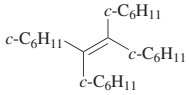
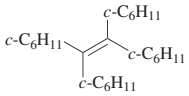
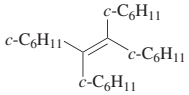
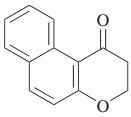
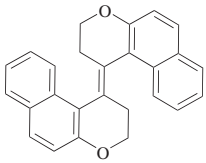
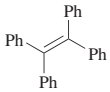
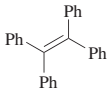
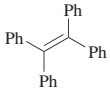
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_4$, Zn, CH_2Cl_2/THF, rt, 30 min 2. rt	 (67)	202
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, 40 h	 **I** + **II** + **III** + **IV** (46)	191
	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 1 h	 (35), (*E*)/(*Z*) = 65:35 + (50)	69
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. Reflux, 6.5 h	 (78)	67
	1. $TiCl_3$, K, THF, reflux, 1 h 2. Reflux, 10 h	 (20)	459
	—	 (—)	460
	1. $TiCl_4$, Zn, py, dioxane, −10 to −5° 2. Microwave irradiation, 10 min	 (75)	121
	Ti powder, TMSCl, DME, reflux, 72 h	 (83)	83
	$TiCl_2(THF)_2$, THF, reflux, 24 h	 (58)	34
	1. $TiCl_3$, M, solvent, reflux, time 2. Reflux, 16 h	 M Solvent Time Li DME 1 h (96) K THF 40 min (80)	27

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

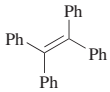
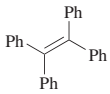
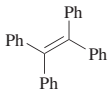
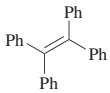
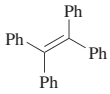
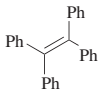
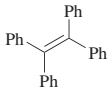
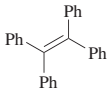
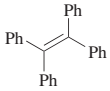
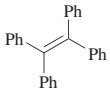
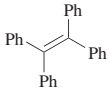
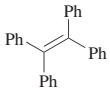
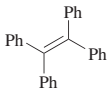
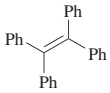
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}	1. $TiCl_3$, K, naphthalene, THF, reflux, 3 h 2. rt, 7 h	 (78)	67
	1. $TiCl_3$, Li, THF, reflux, 3 h; then KCl, reflux, 1 h 2. rt, 5 h	 (75)	114
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, time	 Time (h): 2 (87); 12 (91)	73 84
	$TiCl_n$, Zn, THF, reflux	 *n* Time (h): 3 4 (78); 4 5 (97)	7 3
	1. $TiCl_3$, $LiAlH_4$, THF, 0°, 10 min; then reflux, 30 min 2. Reflux, 20 h	 (90)	120
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (95)	5
	1. $TiCl_4$, Na/Hg, DME, reflux, 4 h 2. Reflux, 12 h	 (84)	84
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 20 min 2. Tertiary amine, reflux, 3 h	 Tertiary amine: Bu_3N (90); Proton Sponge[h] (90)	110
	1. $TiCl_4$, M, THF, temp, time 2. rt, 6 h	 M Temp Time (h): Li reflux 40 (75); K reflux 8 (>80); Mg reflux 3 (>85)	65
	1. $TiCl_4$, $LiAlH_4$, THF, 0°, 30 min; then reflux, 10 min 2. rt, 6 h	 (90)	65
	1. $TiCl_4$, Zn, py, dioxane, −10 to −5° 2. Microwave irradiation, 5 min	 (97)	121
	$TiCl_4$, Zn, 120°, 10 h	 (87)	311
	$TiCl_4$, Hg/Mg, THF, 0°, 2 h; then reflux, 24 h	 (87)	331
	$AlCl_3$, Zn, MeCN, reflux, 16 h	 (77)	88

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

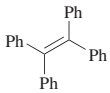
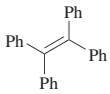
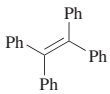
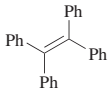
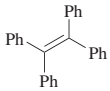
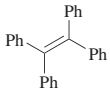
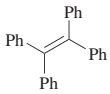
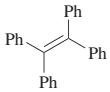
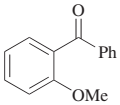
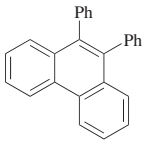
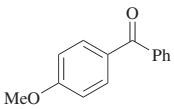
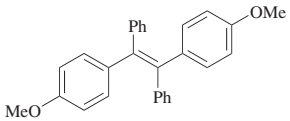
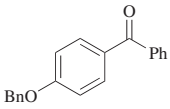
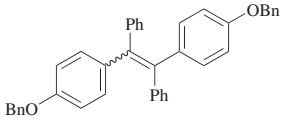
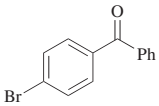
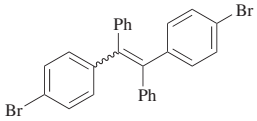
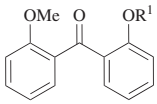
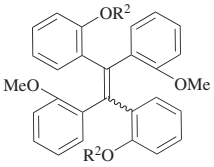
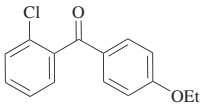
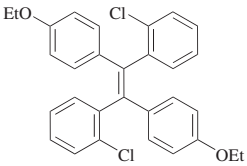
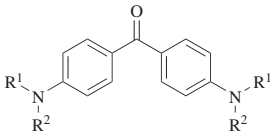
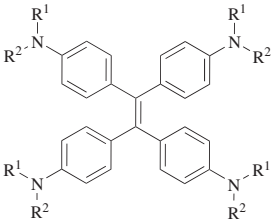
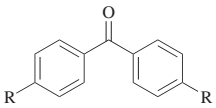
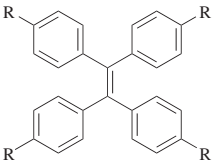
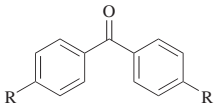
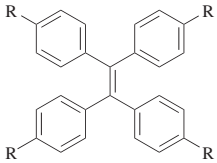
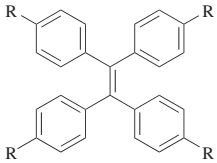
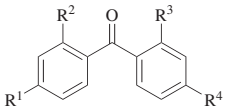
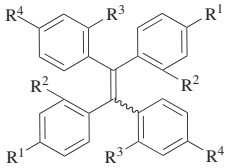
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	Zn, $AlBr_3$, MeCN, 35°, ultrasonication, 12 h	 (57)	89
	[bmim]Cl($AlCl_3$),[f] Zn, rt, 30 min	 (78)	46
	1. $NbCl_5$, K, DME, 80°, 30 min 2. Reflux, 24 h	 (78)	96
	1. $NbCl_5$, $NaAlH_4$, THF/benzene, 0°, 10 min 2. Reflux, 2 h	 (75)	95
	$InCl_3$, Zn, MeCN, reflux, 6 h	 (80)	104
	WCl_5, $LiAlH_4$, THF, rt, 6 h	 (43)	45
	WCl_6, electroreduction,[e] THF, 4 h	 (50.8)	103
	1. UCl_4, $Li_2Np(TMEDA)_2$, xylene, rt, 1 h 2. rt, 1 h; then 70°, 12 h	 (53)	17
	$TiCl_3$, Li, THF	 (36)	332
	$TiCl_3/AlCl_3$, Zn, THF, reflux, 20 h	 (91)	461
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 0.5 h	 (41), (*E*)/(*Z*) = 1:1	55
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 20 h	 (78)	418

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	$TiCl_3$, Zn/Cu, DME, 80°, 14 h	 (*E*)/(*Z*) = 1:1 R^1 / R^2: Me / Me (76); *t*-Bu / H (45, 64[i]); $CH_2{=}CHCH_2$ / $CH_2{=}CHCH_2$ (48); *t*-$BuPh_2Si(CH_2)_2$ / *t*-$BuPh_2Si(CH_2)_2$ (69); $Ph_3Si(CH_2)_2$ / $Ph_3Si(CH_2)_2$ (57)	462
	1. $TiCl_4$, Zn, py, dioxane, −10 to −5° 2. Microwave irradiation, 10 min	 (81)	121
	$TiCl_4$, Zn, dioxane, reflux, 2–5 h	 R^1 / R^2: $-(CH_2)_2O(CH_2)_2-$ (81); H / 4-$MeOC_6H_4$ (72); Me / Ph (77); Me / 4-$MeOC_6H_4$ (83)	463
	$TiCl_4$, Zn		

R	Additive	Solvent	Temp(°)	Time (h)		Refs.
Cl	—	—	120	10	(52)	311
$Br(CH_2)_2O$	—	THF	reflux	20	(63)	464
PhO	py	THF	60	18	(34)	465
MeO	py	CH_2Cl_2/THF	50	20	(68)	466
MeO	py	CH_2Cl_2/THF	0–50	24	(70)	467
n-$C_{10}H_{21}O$	py	CH_2Cl_2/THF	50	20	(77)	466
3,4,5-(*n*-C_8H_{17})$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(55)	468
3,4,5-(*n*-C_9H_{19})$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(57)	468
3,4,5-(*n*-$C_{10}H_{21}$)$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(49)	468
3,4,5-(*n*-$C_{11}H_{23}$)$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(51)	468
3,4,5-(*n*-$C_{12}H_{25}$)$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(34)	468
3,4,5-(*n*-$C_{16}H_{33}$)$_3C_6H_2O$	py	CH_2Cl_2/THF	60	20	(61)	468
CF_3CONH	py	CH_2Cl_2/THF	60	20	(43)	465
n-C_4H_9(Me)CHCONH	py	CH_2Cl_2/THF	60	20	(26)	465
2,4-$Me_2C_6H_3CONH$	py	CH_2Cl_2/THF	60	20	(29)	465

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux	 R — Time (h) H — 6 — (92) — 34 — (90)	144
	$TiCl_4$, Zn, THF, microwave irradiation, 110°, 10 min	 R H (96) *t*-BuS (82)	317
$C_{13–15}$			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 14 h 2. Temp		469

R^1	R^2	R^3	R^4	Temp		(*E*)/(*Z*)
H	MeO	H	H	rt	(36)	1:17
H	MeO	H	H	reflux	(67)	1:13
H	MeO	MeO	H	rt	(76)	—
MeO	H	MeO	H	rt	(76)	1:8
MeO	MeO	H	H	rt	(76)	1:8
H	MeO	Me	H	rt	(26)	—
H	MeO	H	CF_3	rt	(31)	1:9
H	MeO	H	CF_3	reflux	(67)	1:6
H	Me	Me	H	reflux	(70)	—
MeO	Me	Me	MeO	reflux	(85)	—

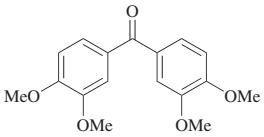
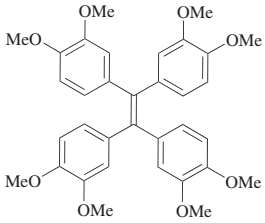
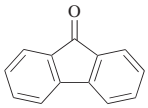
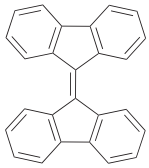
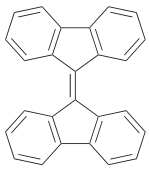
C_{13}			
	$TiCl_4$, Zn, THF, reflux, 12 h	 (92)	470
	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Reflux, 4 h	 (94)	83
	$TiCl_2(THF)_2$, THF, reflux, 24 h	 (44)	34

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

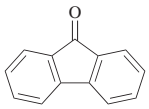
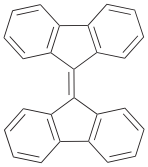
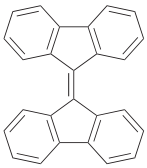
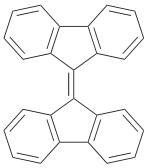
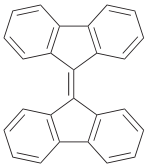
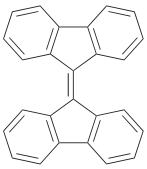
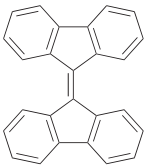
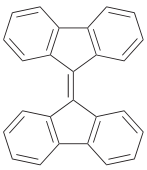
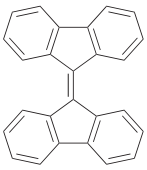
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_3$, Li, THF, ultrasonication, 30°, 1 h 2. Ultrasonication, 30°, 1 h	 (65)	312
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (85)	27
	1. $TiCl_3$, $LiAlH_4$, THF 2. Reflux, 4 h	 (95)	5
	$TiCl_3$, Zn, DME, reflux, 2 h	 (92)	7, 471
	1. $TiCl_4$, Zn, THF 2. Reflux, 16 h	 (38)	430
	$TiCl_4$, Zn, 120°, 10 h	 (54)	311
	1. $TiCl_4$, Zn, py, dioxane, –10 to –5° 2. Microwave irradiation, 5 min	 (94)	121
	$TiCl_4$, Hg/Mg, THF, 0°, 2 h; then reflux, 24 h	 (85)	331

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

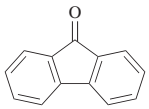
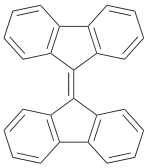
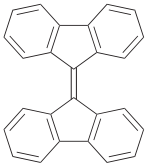
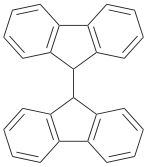
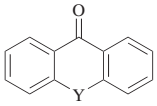
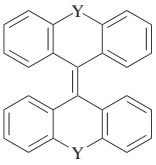
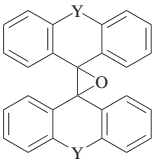
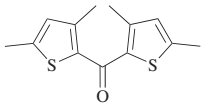
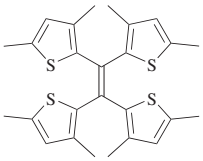
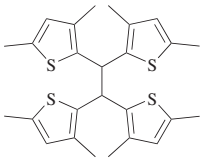
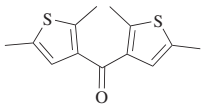
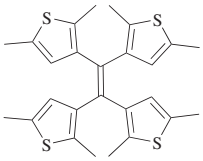
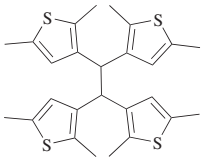
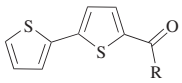
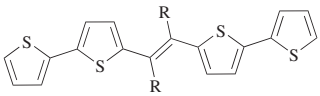
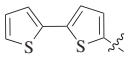
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	VCl, THF, 20–30°, 12 h	 (99)	94
	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Temp, time	 +  **I** **II** Temp / Time (h) / **I** / **II** reflux / 1 / (2) / (74) rt / 20 / (34) / (45)	69
	M, $AlCl_3$, MeCN, ultrasonication, 35°, 12 h	 +  **I** **II** Y / M / **I** / **II** O / Zn / (51) / (0) O / Al / (50) / (0) S / Zn / (36) / (40) S / Al / (48) / (0) $(CH_2)_2$ / Zn / (34) / (48) $(CH_2)_2$ / Al / (17) / (54)	89
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 6.5 h	 +  **I** **I** + **II** (70), **I/II** = 4.5:1 **II**	472
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux, 7.5 h	 +  (58) (—)	472
C_{13-17}			
	1. $TiCl_4$, Zn, CH_2Cl_2/THF, rt, 6 h 2. Py, reflux, 72 h	 R 2-thienyl (95) Ph (93)  (84)	473

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

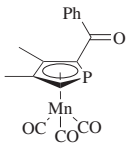
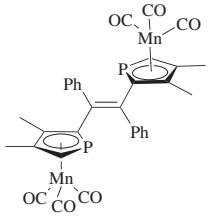
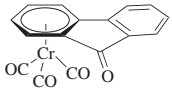
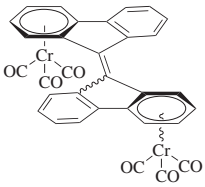
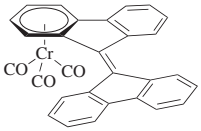
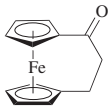
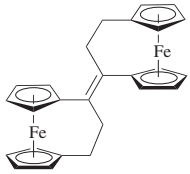
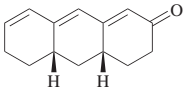
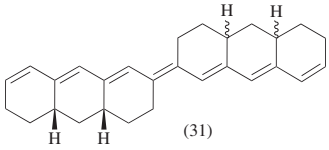
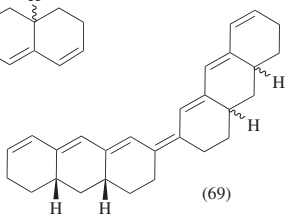
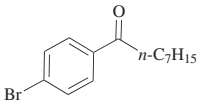
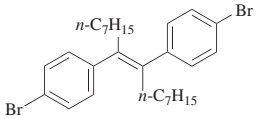
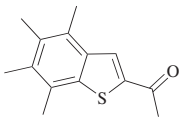
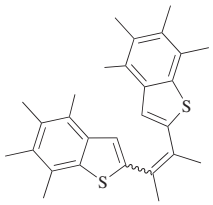
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 48 h	 (41)	208
	$NbCl_3$, THF, rt, 24 h	 (37)[j] +  (43)	97
	$TiCl_3$, Zn, py, DME, reflux, 20 h	 (70)	112
C_{14}			
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 5 min	 (31) +  (69)	403
	1. $TiCl_4$, Zn, py, THF, reflux 2. Reflux, then addition of ketone over 1 h; then reflux, 5 h	 (82)	319
	1. $TiCl_4$, Zn, THF, reflux, 2h 2. Py, reflux, overnight	 (99)	474

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

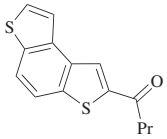
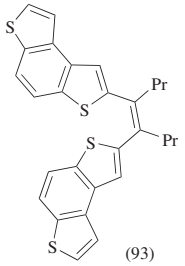
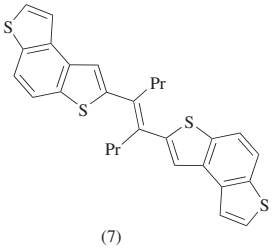
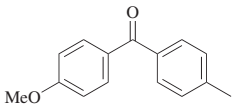
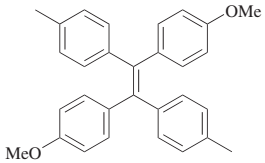
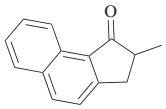
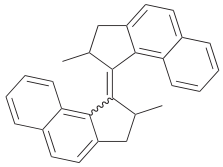
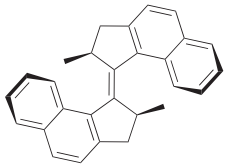
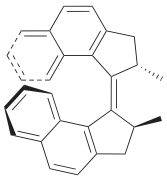
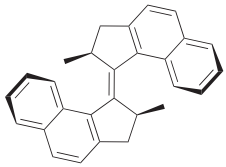
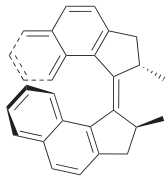
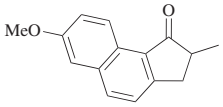
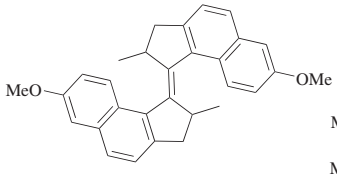
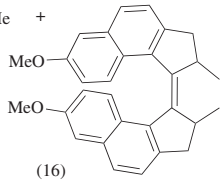
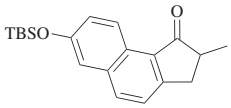
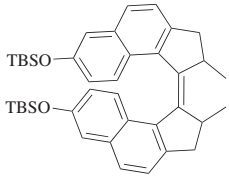
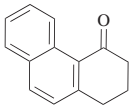
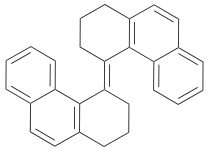
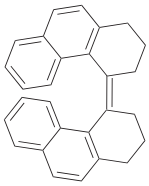
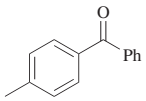
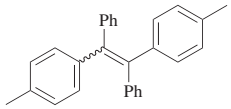
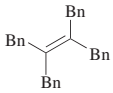
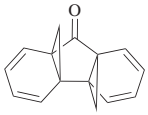
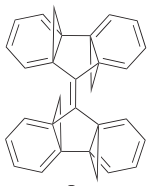
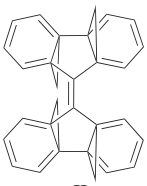
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	$TiCl_4$, Zn, THF, reflux, 3.5 h	 (93) +  (7)	217
	$TiCl_4$, Zn, THF, reflux, 12 h	 (91)	475
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 d	 (76), (*E*)/(*Z*) = 2:5	477
	1.$TiCl_3$, $LiAlH_4$, THF, reflux, 1.5 h 2. Reflux, 96 h	 (14) +  (6)	127
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 4 h 2. Reflux, 3 h	 $(21)^k$ +  $(5)^k$	127
	1. $TiCl_4$, Zn,THF, reflux, 1.5 h 2. Reflux, 18 h	 (18) +  (16)	478

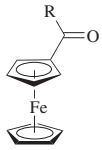
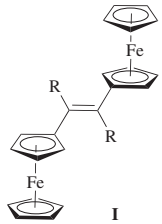
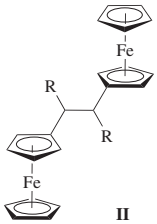
TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 18 h	 (90), (*E*)/(*Z*) = 1:2	478
	1. $TiCl_3$, $LiAlH_4$, THF, 0°, 10 min 2. Reflux, overnight	 (8.3) +  (2.5)	479
	$TiCl_4$, Zn, 120°, 10 h	 (25)	311

C_{15}

	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, time		69
	1. $TiCl_4$, Zn, THF, py, 0° 2. Reflux, 20 h	 (80)	111
	$TiCl_4$, Zn, py, THF, reflux, 20 h	 **I** +  **II** **I + II** (69), **I/II** = 9:1	480

$C_{15–18}$

	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, time	 **I** +  **II**	481

R	Time (h)	**I**	**II**
2-furyl	18	(17)	(—)
3,4-$Cl_2C_6H_3$	24	(8)	(—)
3-MeC_6H_4	37	(7)	(16)
4-MeC_6H_4	20	(10)	(18)

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

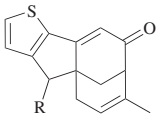
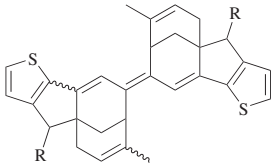
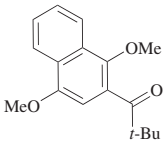
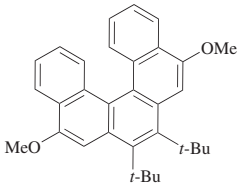
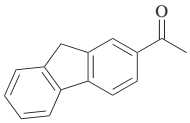
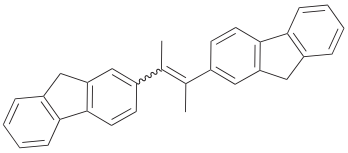
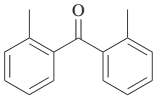
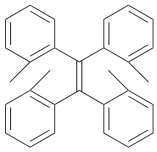
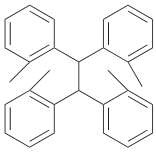
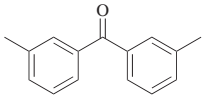
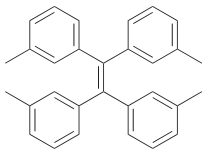
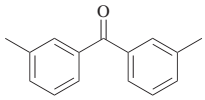
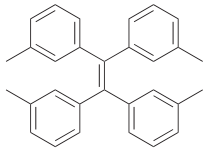
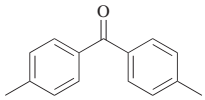
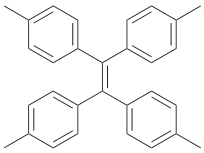
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-19}			
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 30 min	 R: H (89); Bu (48)	450
C_{15}			
	1. $TiCl_3$, $LiAlH_4$, THF, rt 2. Reflux, 3 h	 (1.8)	452
	$TiCl_4$, Zn, py	 (—)	482
	1. $TiCl_3$, $LiAlH_4$, THF, 0°, 10 min 2. rt, 20 h	 (15) +  (40)	483
	$TiCl_3$, $LiAlH_4$, THF	 (70)	484
	$TiCl_4$, Zn, THF	 (98)	484, 485
	$TiCl_4$, Zn, 120°, 10 h	 (21)	311

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

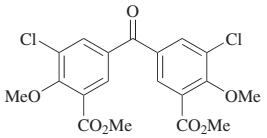
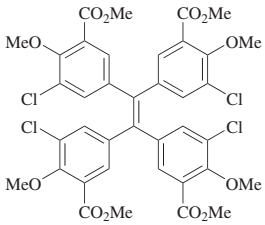
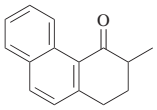
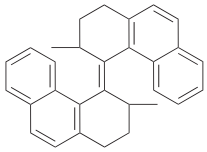
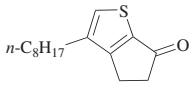
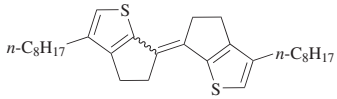
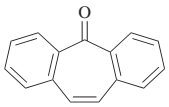
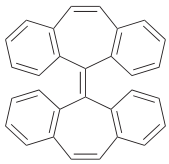
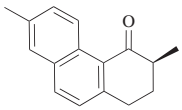
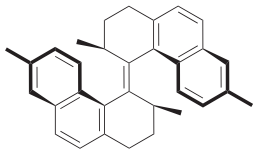
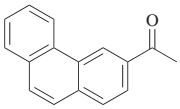
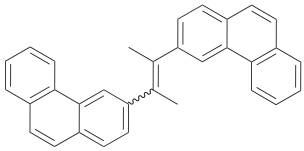
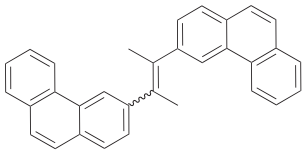
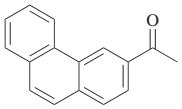
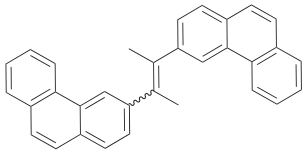
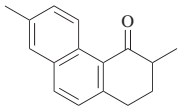
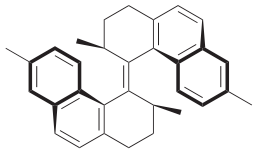
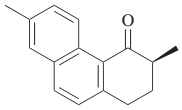
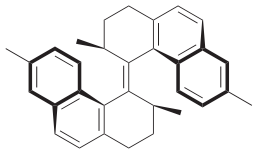
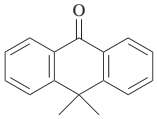
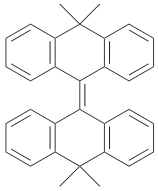
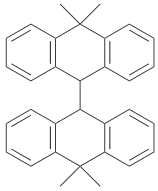
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}			
	$TiCl_4$, Zn, THF, reflux, 2 h	 (53)	486
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 20 h	 (8)	487
	1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Reflux, 5 h	 (65), (*E*)/(*Z*) = 5:1	393
	1. $TiCl_4$, Zn, THF, rt, 1h; then reflux, 5 h 2. Py, 0°, then addition of ketone over 4 h; then reflux, 36 h	 (11)	488
C_{16}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 40 h	 (30)	476
	1. $TiCl_3$, $LiAlH_4$, THF, rt, 1 h 2. Reflux, 24 h	 (67), (*E*)/(*Z*) = 1:4	98
	$W(CO)_6$	 (12), (*E*)/(*Z*) = 1:4	98

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}			
	Zn, TMSCl	 (38), (*E*)/(*Z*) = 1:4	98
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 7 d	 (9)	489
	$TiCl_4$, Zn, THF	 (30)[k]	490
	1. $TiCl_4$, Zn, THF, rt, 1 h; then reflux, 5 h 2. Py, 0°, 3.5 h; then reflux, 48 h	 +  **I** **II**	**I** + **II** (66), **I/II** = 1:3	491

C_{17}

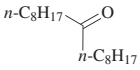
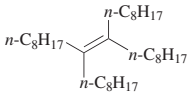
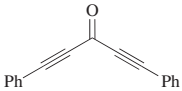
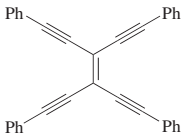
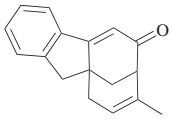
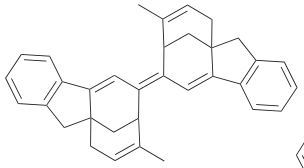
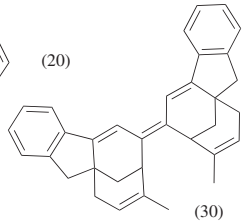
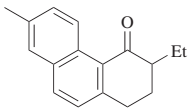
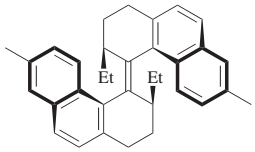
	1. $TiCl_4$, Zn, solvent , reflux, 30–40 min 2. Reflux, time		Solvent / Time (h) THF/toluene / 1.5 / (70) dioxane / 6 / (75)[l]	313
	$TiCl_4$, Zn, THF, reflux, 5 d	 (2.2)		492
	$TiCl_4$, Zn, THF, reflux, 2 h	 (20) +  (30)		493
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 7 d	 (7.2)		489

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

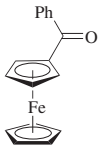
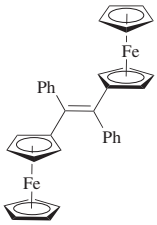
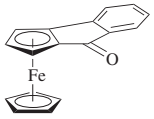
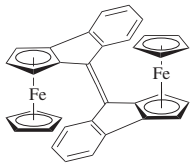
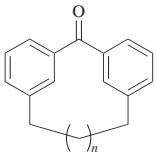
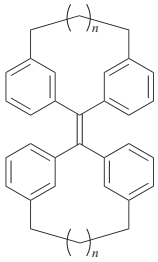
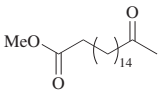
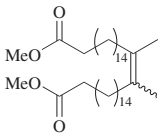
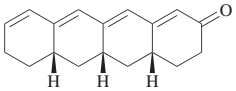
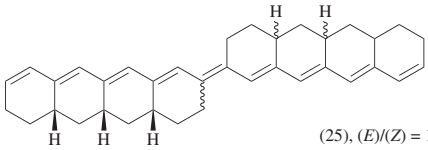
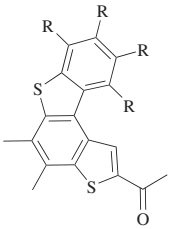
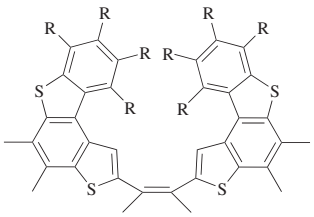
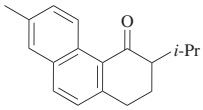
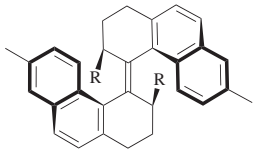
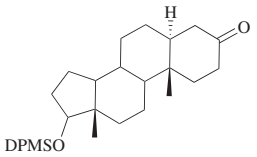
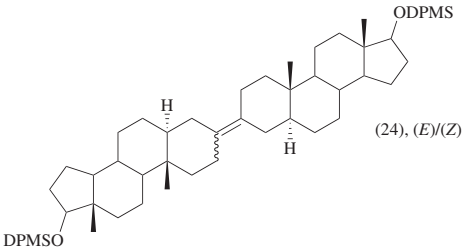
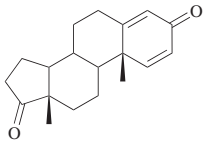
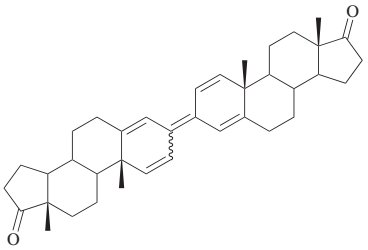
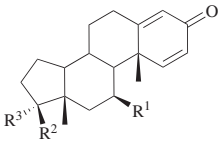
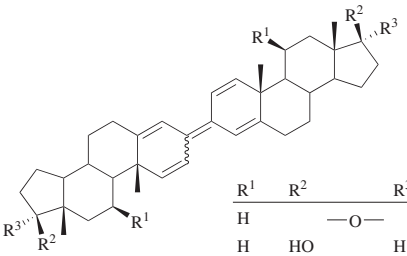
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17}			
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 2 h 2. Bu_3N, reflux, 17 h	 (23)	481
	Zn, TMSCl, THF, 0°, 2 h	 (76)[j]	92
$C_{17–19}$			
	$TiCl_4$, Zn, THF	 *n*: 2 (90); 3 (94); 4 (98)	485
C_{18}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 12 h	 (69)	494
	1. $TiCl_4$, Zn, THF, –15° to reflux; then py, reflux, 15 min 2. Reflux, 15 min	 (25), (*E*)/(*Z*) = 15:85	204
$C_{18–22}$			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, overnight	 R: H (quant); Me (quant)	474
C_{18}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 7 d	 (0.41) R = *i*-Pr	489

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{19}			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 15 min 2. Reflux, 20 h	 (24), (*E*)/(*Z*) = 1:1	495
	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Reflux, 1 h	 (84), (*E*)/(*Z*) = 1:1	83
C_{19-21}			
	Zn, HCl, THF, reflux, 10 h		90

R^1	R^2		R^3	(*E*)/(*Z*)
H		—O—	(97)	3:2
H	HO		H (96)	—
H	$AcOCH_2CO$		HO (85)	—
AcO	$AcOCH_2CO$		HO (83)	—

C_{21}

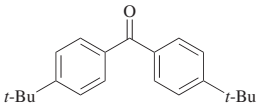
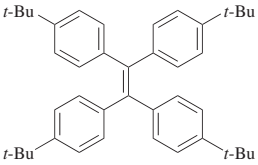
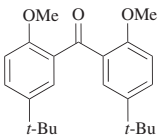
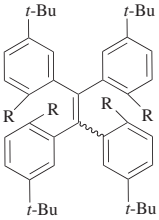
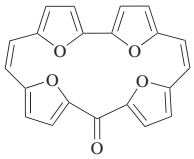
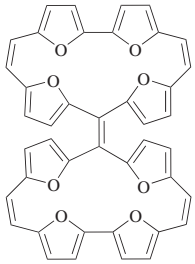
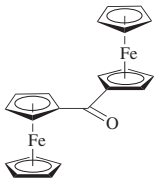
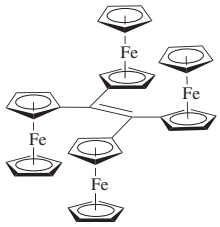
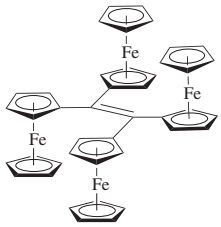
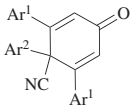
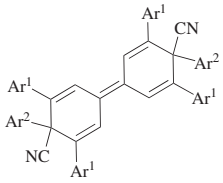
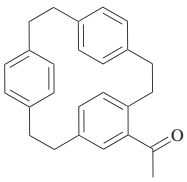
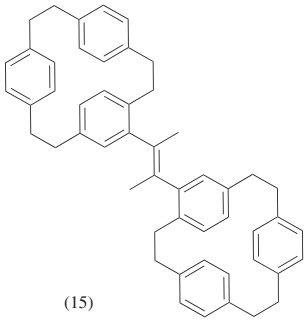
	$TiCl_4$, Zn, THF, 60°, 1 h	 (79)	496
	1. $TiCl_3$, Zn/Cu, DME, reflux, 14 h 2. rt	 (84) R = MeO	469

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21}			
	1. $TiCl_4$, Zn/Cu, THF, reflux, 30 min 2. Reflux, 2 h	 (43)	497
	Zn, TMSCl, THF, 0°, 2 h	 (73)	92
	1. $TiCl_3(THF)_3$, Li, DME, ultrasonication, 30 min 2. Ultrasonication, 30 min	 (75)	206
C_{25-27}			
	$TiCl_4$, Li, THF, reflux		130
C_{26}			
	$TiCl_4$, Zn, py, THF, heat	 (15) + (22)	498

Ar^1	Ar^2	Time (h)	
Ph	Ph	6	(85)
Ph	$4\text{-}O_2NC_6H_4$	8	(45)
$4\text{-}MeC_6H_4$	$4\text{-}O_2NC_6H_4$	8	(80)
$4\text{-}MeC_6H_4$	$4\text{-}ClC_6H_4$	10	(82)

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

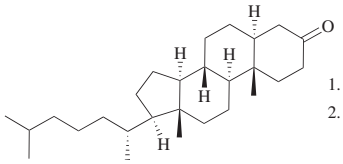
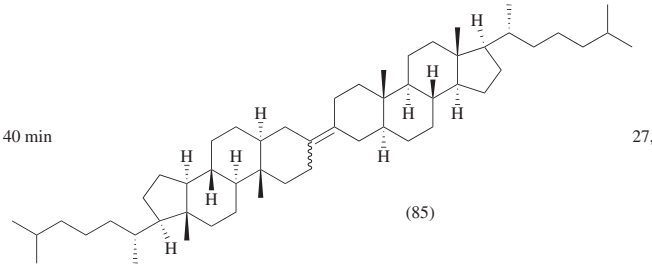
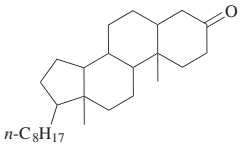
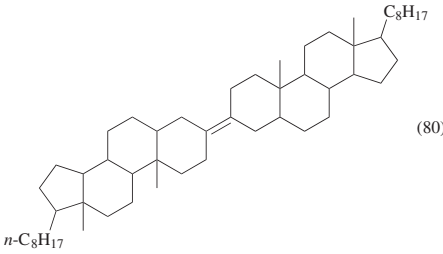
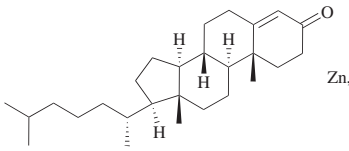
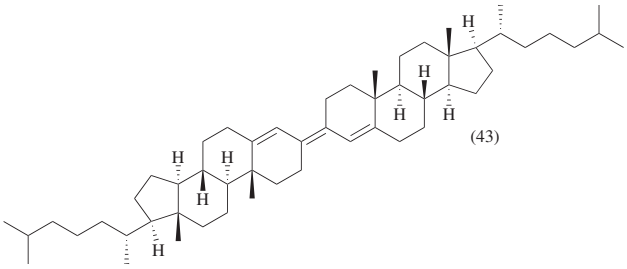
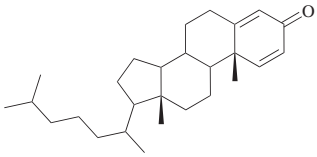
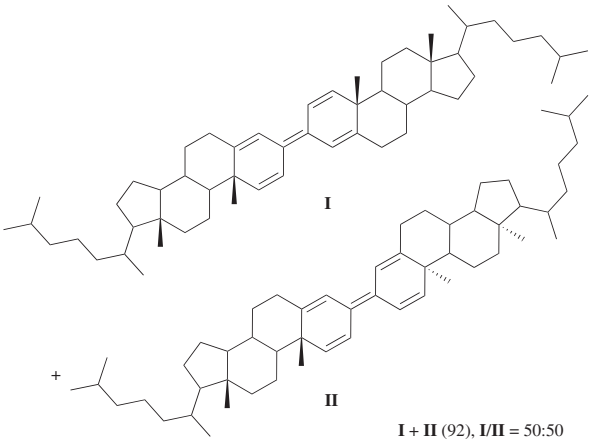
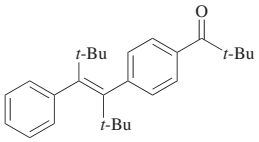
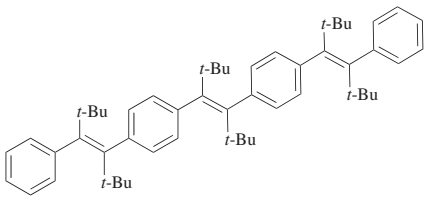
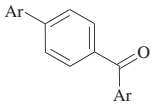
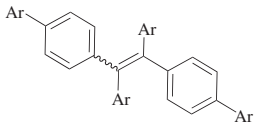
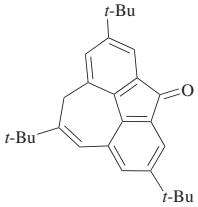
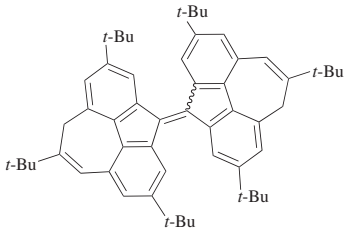
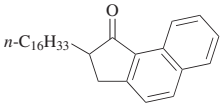
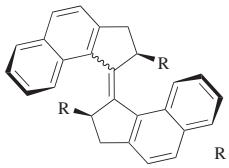
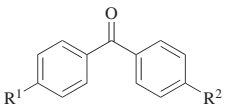
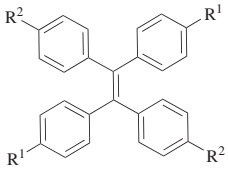
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{27}			
	1. $TiCl_3$, K, THF, reflux, 40 min 2. Reflux, 16 h	 (85)	27, 62
	$TiCl_4$, Hg/Mg, THF 0°, 2 h; then reflux, 24 h	 (80)	331
	Zn, TMSCl, THF	 (43)	91
	1. $TiCl_4$, Zn, py, THF, 0° 2. 0°, 30 min	 **I** + **II** (92), **I**/**II** = 50:50	440

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{27}			
	$TiCl_4$, Zn, THF	 (—)	499
 Ar = 4-*t*-BuC_6H_4	$TiCl_4$, Zn, THF, 60°, 1 h	 (63)	500
C_{28}			
	$TiCl_4$, Zn/Cu, THF, reflux, 1 h	 (99), (*E*)/(*Z*) = 1:1	501
C_{29}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 d	 R = *n*-$C_{16}H_{33}$ (76), (*E*)/(*Z*) ~3:2	502
$C_{31–41}$			
	$TiCl_4$, Zn, THF		

R^1	R^2	Temp(°)	Time (h)		Refs.
3,5-$Ph_2C_6H_3$	Br	–40 to reflux	5	(24)	503
4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	60	1	(63)	504, 500
anthracen-9-yl	anthracen-9-yl	60	1	(56.7)	504

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

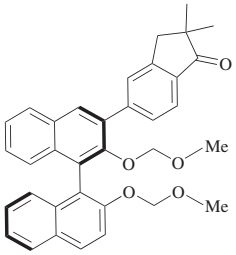
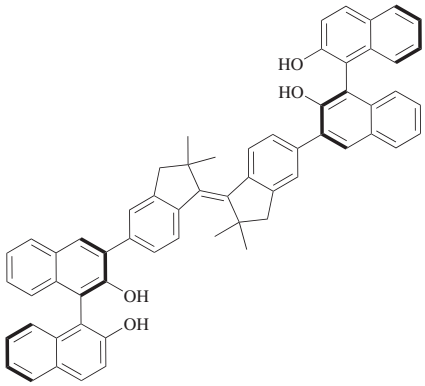
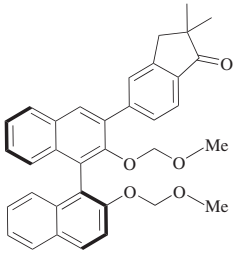
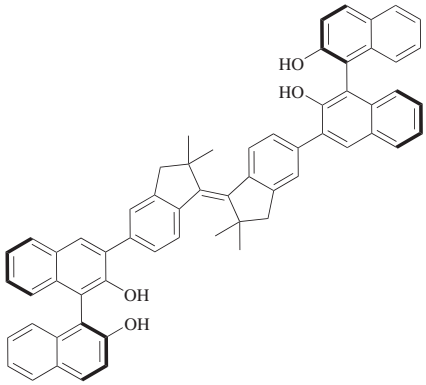
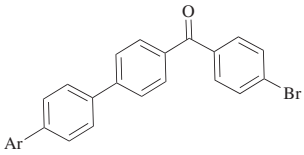
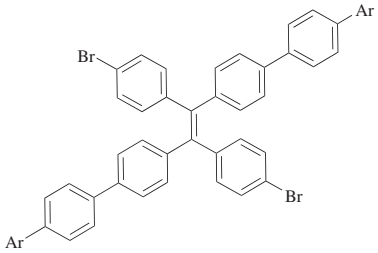
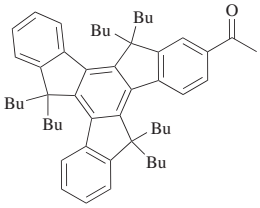
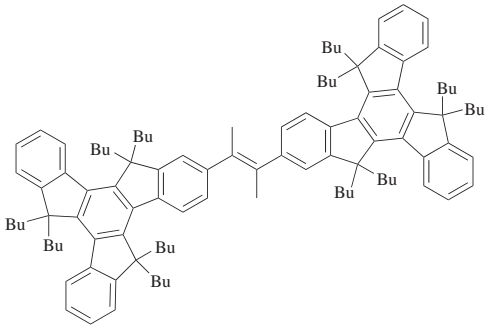
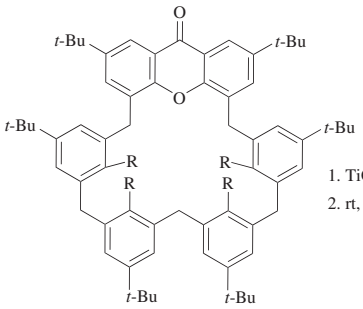
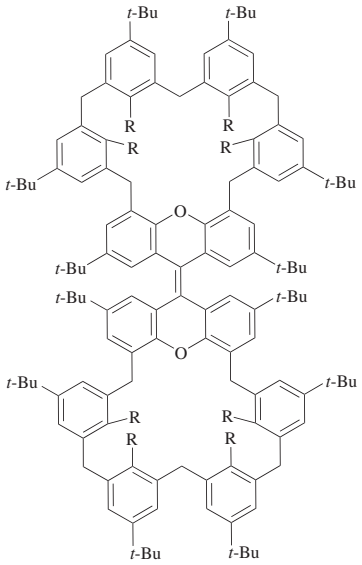
Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{31}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 12 h 3. 6 N HCl, CH_2Cl_2/MeOH, reflux, 12 h	 (29)	505
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 12 h 3. 6 N HCl, CH_2Cl_2/MeOH, reflux, 12 h	 (21)	505
C_{49}			
 Ar = 3,5-(4-PhC_6H_4)$_2C_6H_3$	$TiCl_4$, Zn, THF, –40° to reflux, 5 h	 (—)	503
C_{53}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 d	 (93)	506

TABLE 1B. HOMOCOUPLING OF KETONES (*Continued*)

Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{66}			
 R = MeO	1. $TiCl_4$, $LiAlH_4$, THF, rt, 40 min 2. rt, 2 h; then reflux, 24 h	 (28)	507

[a] The (*E*)-isomer was separated in 5.8% yield by PGC.

[b] A commercial McMurry reagent ($TiCl_3$/$LiAlH_4$) was used.

[c] The product is a mixture of four diastereomers.

[d] The product was isolated as a THF complex.

[e] The electroreduction was carried out at $V \leq -1900$ mV/SCE.

[f] [bmim]Cl($AlCl_3$) is 1-butyl-3-methylimidazolium chloroaluminate.

[g] The ratio of β-*syn*: α-*syn*: β-*anti*: α-*anti* is given.

[h] The Proton Sponge is *N,N,N,N*-tetramethyl-1,8-diaminonaphthalene.

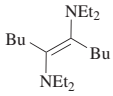
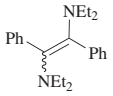
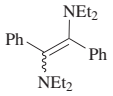
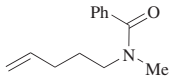
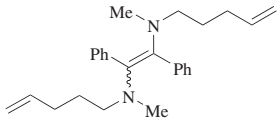
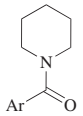
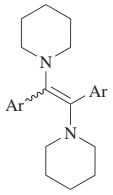
[i] $TiCl_3(DME)_{1.5}$ was used as the titanium source.

[j] The product is a mixture of (*E*)/(*Z*)-*syn*/*anti* isomers.

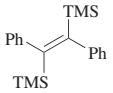
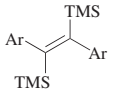
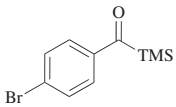
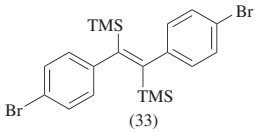
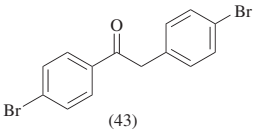
[k] Optically active starting material was employed.

[l] The yield is based on the amount of ketone consumed.

TABLE 1C. HOMOCOUPLING OF MISCELLANEOUS COMPOUNDS

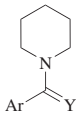
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5			
	Sm, SmI_2, HMPA/toluene, reflux, 26 h	 (23)	105
C_7			
	Sm, SmI_2, THF, 67°, 2–4 h	 (72), (*E*)/(*Z*) = 38:62	105
	1. Yb, ICH_2CH_2I, THF, 67°, 1 h 2. 67°, 4 h	 (45), (*E*)/(*Z*) = 40:60	108
	Sm, SmI_2, THF, 67°, 2–4 h	 (12), (*E*)/(*Z*) = 47:53 + (41)	105
C_{7-11}			
	Sm, SmI_2, THF, 67°, 2–4 h		105

Ar		(*E*)/(*Z*)
4-ClC_6H_4	(50)	84:16
1-Np	(50)	34:66
2-Np	(67)	87:13

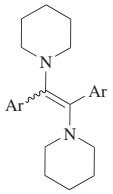
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	$TiCl_3$, Na/Al_2O_3, DME, 20°, 2.5 h	 (66)	131
	1. $TiCl_3$, Na/Al_2O_3, solvent, reflux, 1 h 2. Reflux, 1 h		70
	1. $TiCl_3$, Na/NaCl, THF, reflux, 1 h 2. Reflux, 1 h	 (33) +  (43)	70

Ar	Solvent	
Ph	DME	(67)
4-$MeOC_6H_4$	THF	(56)

C_{7-11}



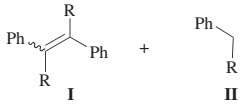
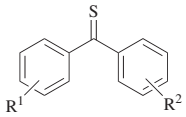
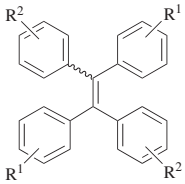
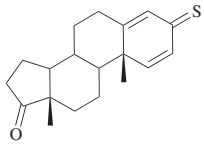
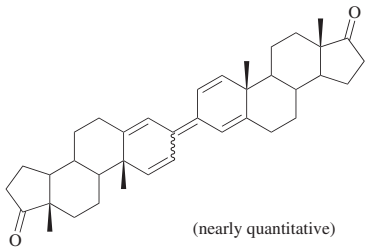
1. M, ICH_2CH_2I, THF, 67°, 1 h
2. 67°, 4 h



Y	Ar	M		(*E*)/(*Z*)
O	4-MeC_6H_4	Yb	(42)	89:11
O	1-Np	Yb	(34)	—
S	Ph	Yb	(67)	—
Se	Ph	Yb	(61)	—
S	Ph	Sm	(82)	83:17
Se	Ph	Sm	(78)	—

108

TABLE 1C. HOMOCOUPLING OF MISCELLANEOUS COMPOUNDS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{7-13}	1. $TiCl_3$, Li, THF, reflux, 3 h 2. Py, reflux, 16–18 h	 **I** + **II** R: **I** (42), **II** (—); H: **I** (42), **II** (—); Me: **I** (45), **II** (—); Bu: **I** (32), **II** (38); Ph: **I** (26), **II** (43)	138
C_{13-14} 	Cu, DMSO, rt	 R^1 / R^2: H / H, 31 h, (98), —; 4-F / 4-F, 8 h, (93), —; 4-Cl / 4-Cl, 15 h, (65), —; 4-MeO / 4-MeO, 20 h, (73)[a], —; 4-O_2N / H, 4 h, (49), 1:1; 4-CF_3 / H, 12 h, (98), 1:1; 3-O_2N / H, 22 h, (99), 1:1	139
C_{19} 	Zn, HCl, THF, reflux, 10 h	 (nearly quantitative)	90

[a] The reaction was carried out at 80°.

TABLE 2A. MIXED-COUPLING OF ALDEHYDES

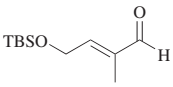
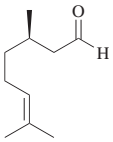
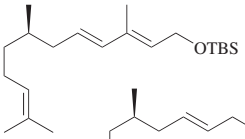
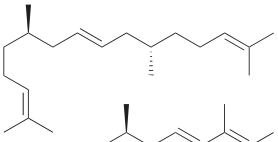
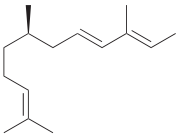
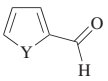
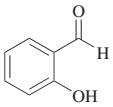
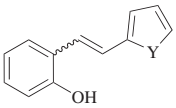
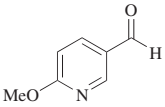
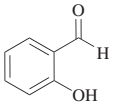
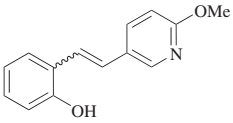
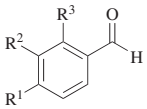
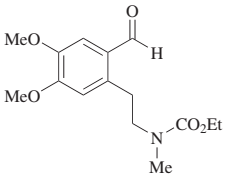
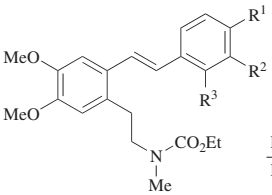
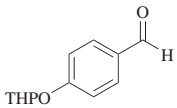
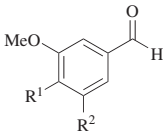
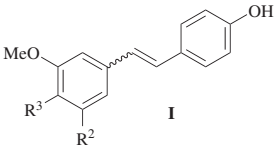
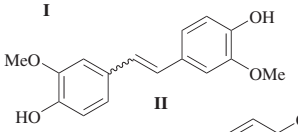
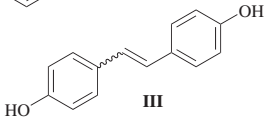
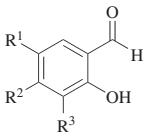
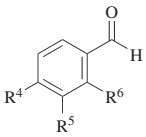
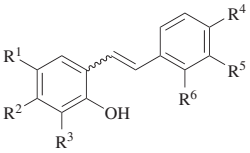
Aldehyde 1	Aldehyde 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 		1. $TiCl_4$, Zn, py, DME, reflux, 2.5 h 2. Reflux, 14 h; then addition of aldehydes; then reflux, 5 h	 (35)[a] +  (5)[a] +  (10.5)[a]	509, 510
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux	 Y: O (58), S (62)	145
C_6 		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux	 (62)	145

TABLE 2A. MIXED-COUPLING OF ALDEHYDES (*Continued*)

Aldehyde 1	Aldehyde 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$TiCl_3$, Li, DME, reflux		511
			R^1 R^2 R^3 H H H (55) –OCH_2O– Br (67)	
		1. $TiCl_3$, Zn, THF, reflux, 3 h 2. Reflux	 **I**	346
			+  **II**	
			+  **III**	

R^1	R^2	R^3	**I**	(*E*)/(*Z*)	**II**	**III**
THPO	H	HO	(25)	45:55	(20)	(15)
H	MeO	H	(22)	48:52	(25)	(19)

C_{7-8}

		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux		145

R^1	R^2	R^3	R^4	R^5	R^6	
H	H	H	H	H	H	(60)
H	H	H	MeO	H	H	(75)
H	H	H	H	–CH=CH-CH=CH–		(61)
H	H	H	H	H	MeO	(65)
H	H	H	–OCH_2O–		H	(63)
H	H	H		H	H	(72)
H	H	H	H	CF_3	H	(52)
Cl	H	H	H	H	H	(59)
Me	H	H	H	H	H	(59)
MeO	H	H	H	H	H	(63)
H	H	MeO	H	H	H	(69)
–OCH_2O–		H	H	H	H	(72)

C_7

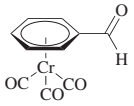
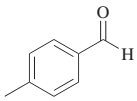
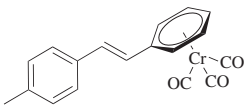
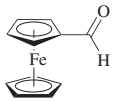
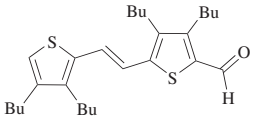
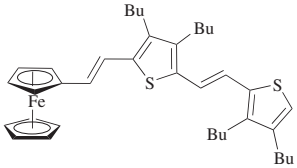
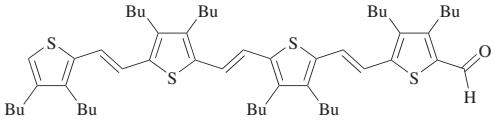
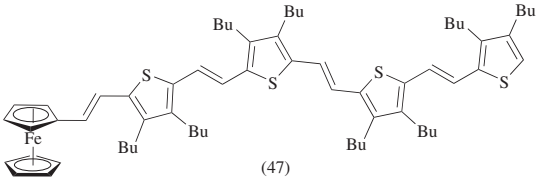
		$NbCl_3$, THF, rt, 8 h	 (71)	97

TABLE 2A. MIXED-COUPLING OF ALDEHYDES (*Continued*)

Aldehyde 1	Aldehyde 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}				
		1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, overnight	 (quant)	387
		1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, overnight	 (47)	387

[a] Optically active starting material was employed.

TABLE 2B. MIXED-COUPLING OF KETONES

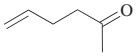
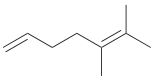
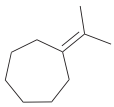
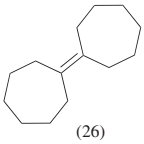
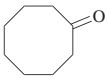
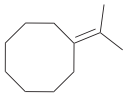
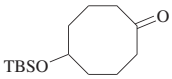
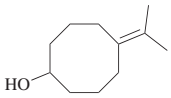
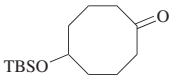
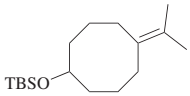
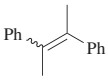
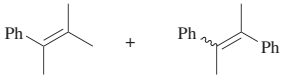
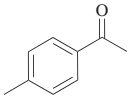
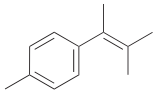
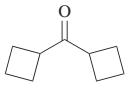
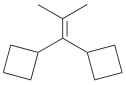
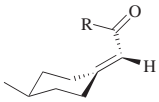
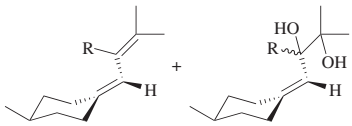
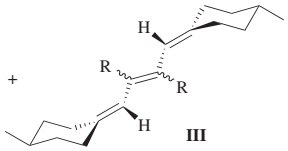
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		$W_2(OCH_2CMe_3)_6(Py)_2$, 22°, 12–22 h	 (36)	99
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (50) +  (26)	27, 141
		$W_2(OCH_2CMe_3)_6(Py)_2$, 22°, 12–22 h	 (44)	99
		1. $TiCl_3(AlCl_3)$, Li, THF, rt, 12 h 2. rt, 5 h; then addition of ketones; then rt, 14 h	 (38)	512
		$TiCl_3(AlCl_3)$, Li, heat	 (52)	513
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	(65) +  (16)	27, 514

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		$InCl_3$, Zn, MeCN, reflux, 13 h	 (65) + (15)	104
		$W_2(OCH_2CMe_3)_6(Py)_2$, 22°, 12–22 h	 (66)	99
		$TiCl_3$, Li	 (30)	185
		1. $TiCl_4$, $LiAlH_4$, THF, reflux, 1 h 2. Temp, time	 **I** + **II**	128
			 + **III**	

R	Temp	Time (h)	**I**	**II**	**III**
Me[a]	0°	1	(—)	(52)	(4)
Ph[a]	rt	3.5	(40)	(24)	(—)

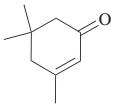
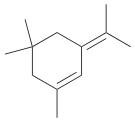
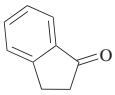
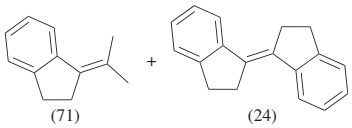
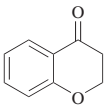
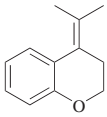
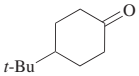
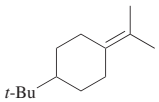
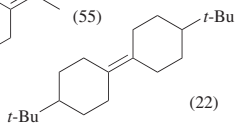
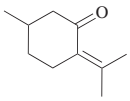
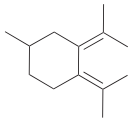
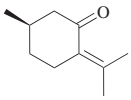
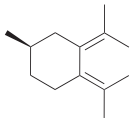
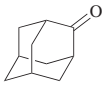
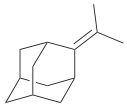
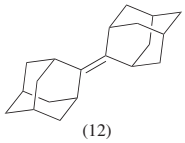
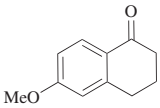
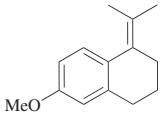
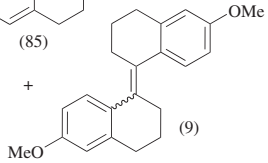
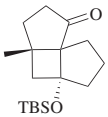
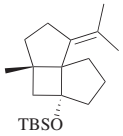
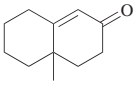
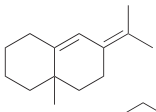
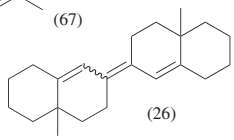
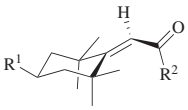
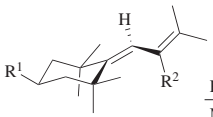
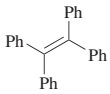
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (63)	27, 141
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (71) + (24)	27, 141
		1. $TiCl_4$, Zn, py, dioxane, −10 to −5° 2. Microwave irradiation, 10 min	 (10)	121
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (55) +  (22)	27, 141

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (55)	27, 141
		—	 (50)	196
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (63) +  (12)	27, 141
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (85) +  (9)	27, 141
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 4 h; then addition of ketones; then reflux, 12 h	 (75.6)	321
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (67) +  (26)	27, 141
		1. $TiCl_4$, $LiAlH_4$, THF, reflux, 1 h 2. 60°, 20 h		128
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	(94) +  (trace)	27, 141

R^1	R^2	
Me	Me	(53)[a]
TBSO	Me	(73)[a]
TBSO	Ph	(85)[a]

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

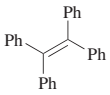
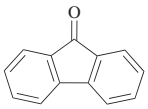
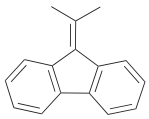
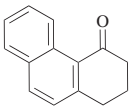
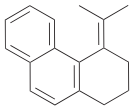
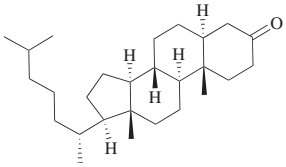
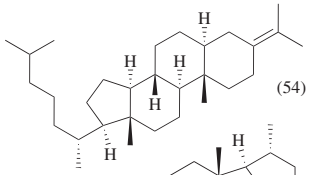
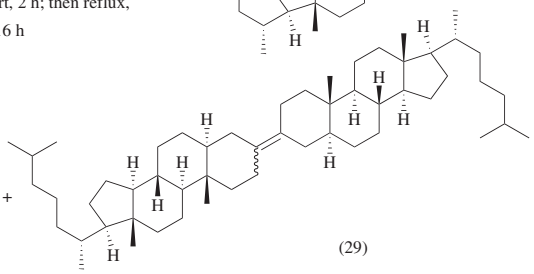
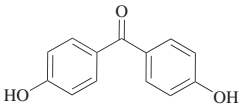
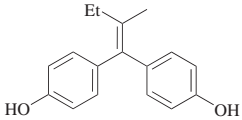
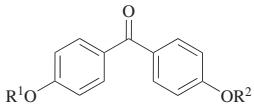
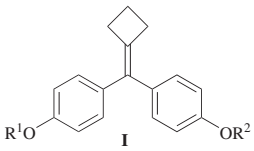
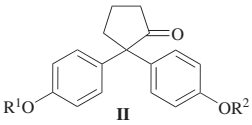
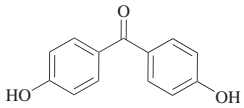
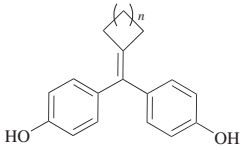
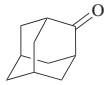
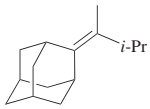
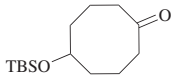
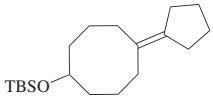
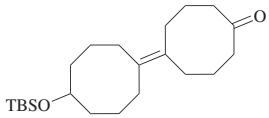
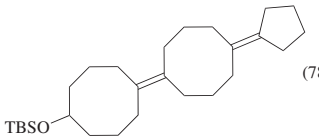
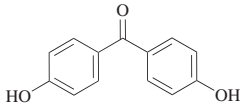
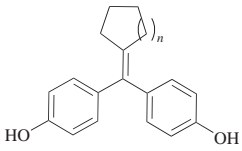
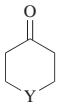
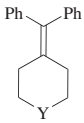
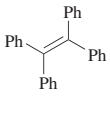
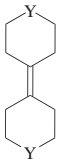
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		$TiCl_3$, Li, DME	(—)	515
		1. $TiCl_4$, Zn, py, dioxane, −10 to −5° 2. Microwave irradiation, 10 min	(52)	121
		MCl_3, Zn, MeCN, reflux	**I** +  **II**	
			M / Time (h) / **I** / **II** Al / 22 / (71) / (24)	88
			In / 18 / (55) / (20)	104
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (84)	27, 141
		$TiCl_3$, $LiAlH_4$, THF, reflux, 2 h	 (31)	516
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (54) +  (29)	27, 141
C_4				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux in the dark, 2 h	 (91)	517

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_4				
		1. $TiCl_4$, M, THF, reflux, 2 h 2. Reflux, time	 **I** +  **II**	189

R^1	R^2	M	Time (h)	**I**	**II**
H	H	Mg/HgCl	4	(18)	(74)
Me	Me	Mg/HgCl	20	(87)	(trace)
Me	H	Zn	2	(18)	(57)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{4-7}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h		518
C_5				
		$TiCl_3$, Li	 (7)	519
		1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 3 h	 (95)	412
		1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 3 h	 (78)	412
C_{5-6}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 4 h		189
		1. $TiCl_4$, Zn,THF, reflux, 2.5 h 2. Py, reflux	 **I** +  **II** +  **III**	144

Y	**I**	**II**	**III**
CH_2	(78)	(2)	(10)
PhN	(92.5)	(5)	(0.5)
$AcHNCH_2$	(90.5)	(4)	(2)

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

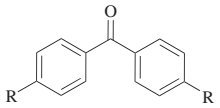
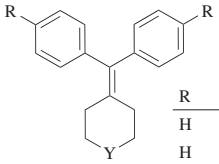
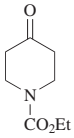
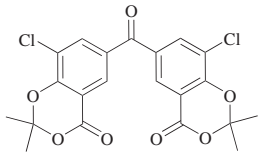
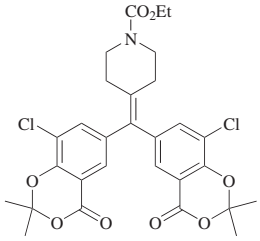
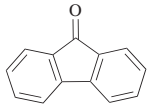
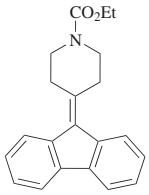
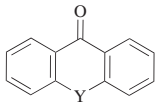
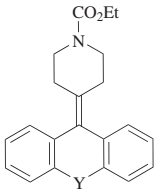
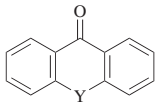
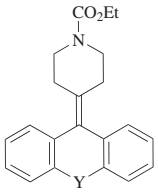
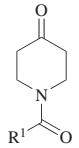
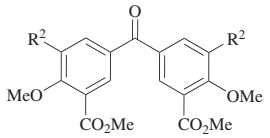
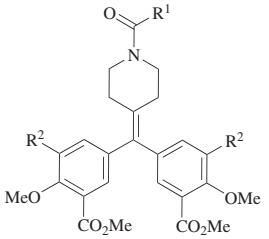
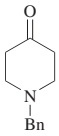
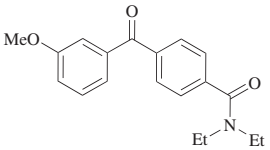
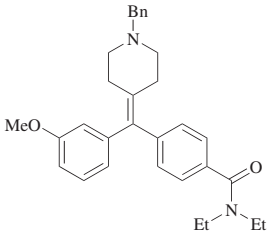
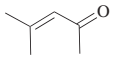
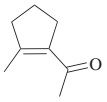
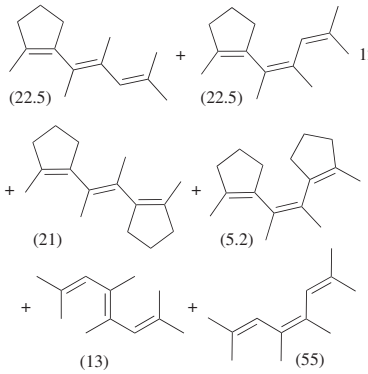
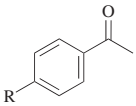
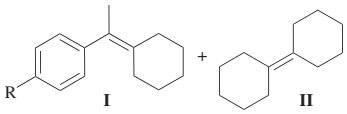
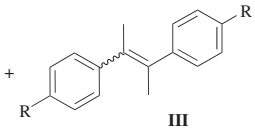
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
		1. $TiCl_3$, Li, DME, reflux, 2 h 2. rt, 4 h; then reflux, 13 h	 R Y H CH_2 (86) H O (93) H S (76) H EtO_2CN (93) HO EtO_2CN (53) AcO EtO_2CN (82) HO CH_2 (87)	520 520 520 521, 520 521 521 521
C_5				
		1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 14 h	 (32.1)	522
		1. $TiCl_3$, Li, DME, reflux, 2 h 2. rt, 4 h; then reflux, 13 h	 (70)	521
		1. $TiCl_3$, Li, DME, reflux, 2 h 2. rt, 4 h; then addition of ketones; then reflux, 13 h	 Y — (52) H, H (93) O (27) S (51) $(CH_2)_2$ (44)	523
		1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 14 h	 Y CH=CH (77.9) $(CH_2)_2$ (80.2)	522

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

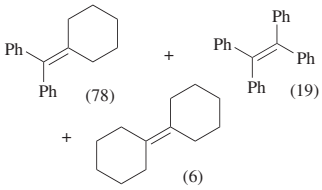
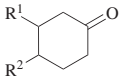
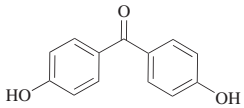
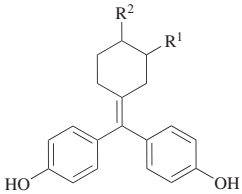
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
		1. $TiCl_4$, Zn, THF, reflux, 1–2 h 2. Reflux, 12–15 h	 R^1 / R^2: MeO / Cl (48.8); MeO / Me (56.4); EtO / Cl (58.3); EtO / Me (61.7); $MeO_2C(CH_2)_3$ / Cl (13.0); $MeO_2C(CH_2)_3$ / Me (14.4)	522
		1. $TiCl_4$, Zn, DME, reflux, 2 h 2. Reflux, 4 h	 (65)	524

C_6

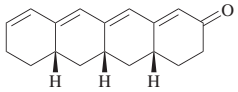
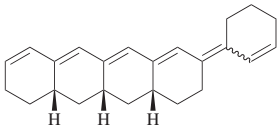
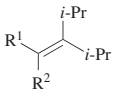
		1. $TiCl_4$, Mg, –60° to rt, 3–4 h; then rt, 20 h 2. Reflux, 15 h	 (22.5) + (22.5) + (21) + (5.2) + (13) + (55)	129
		1. $TiCl_4$ (x eq), Zn, THF, reflux, 2.5 h 2. Py, reflux	 **I** + **II**  **III**	144

R	x	**I**	**II**	**III**
H	5.0	(32)	(29)	(27)
HO	5.0	(30)	(31)	(26)
HO	2.0	(70)	(13)	(8)
MeO	2.0	(69)	(14)	(9)
	2.0	(60)	(17)	(14)

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6				
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (78) + (19) + (6)	27
C_{6-9}				
		1. $TiCl_4$, Zn, THF, reflux, time 1 2. Reflux, time 2		

R^1	R^2	Time 1 (h)	Time 2 (h)		Refs.
MeO_2C	H	2	2	(81)	518, 525
MeO_2CCH_2	H	2	2	(~80)	525
$(MeO_2C)_2CH$	H	2	2	(74)	518
$AcO(CH_2)_3$	H	2	2	(70)	518
HO	H	1	3	(50.4)	526
H	AcO	2	2	(83)	518
H	MeO_2C	2	2	(~80)	525
H	EtO_2C	2	2	(77)	518, 525
H	MeO_2CCH_2	2	2	(71)	518, 525
H	HO	1	3	(58.0)	526

C_6				
		1. $TiCl_4$, Zn, THF, −15° to reflux; then py, reflux, 15 min 2. Reflux, 15 min	 (38)	204
C_7				
		—		

R^1	R^2		Refs.
Me	*i*-Pr	(27)	527
Me	Ph	(—)	527
Et	Ph	(25)	527
i-Pr	Ph	(15)	527
$(CH_3)_2CD$	Ph	(17)	527
i-Bu	Ph	(23)	527
t-Bu	Ph	(4)	527
Me	2-MeC_6H_4	(61)	528

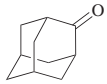
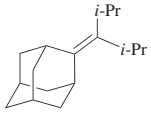
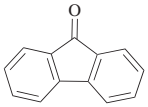
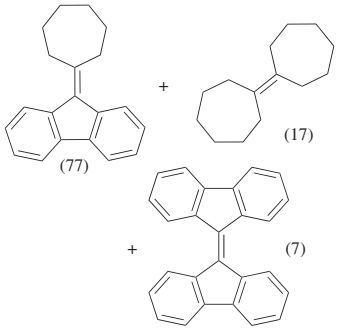
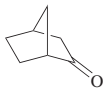
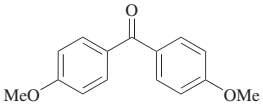
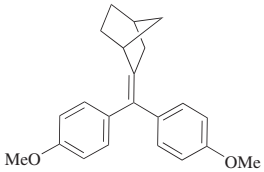
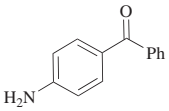
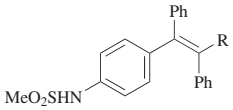
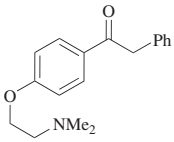
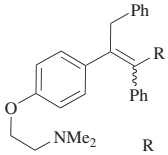
	$TiCl_3$, Li		(7)	519

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (77) + (17) + (7)	27
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux, 1.5 h	 (65)	529
C_{8-15}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt, 15 h		530
C_{8-11}				
		$TiCl_4$, Zn, dioxane, reflux, 4 h		531

R		(*E*)/(*Z*)
Me	(60)	
Et	(63)	
Bu	(64)	
n-C_6H_{13}	(62)	
c-C_6H_{11}	(60)	
n-C_8H_{17}	(65)	

R		(*E*)/(*Z*)
Et	(69)	1:4
Bu	(48)	1:2
$ClCH_2CH_2$	(41)	1:1
$BrCH_2$	(39)	9:1
Me_3CH_2BrCH	(34)	6:1
O_2NCH_2	(42)	1:11
Pr	(46)	1:2
$ClCH_2$	(44)	1:2

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

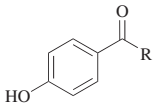
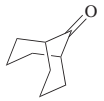
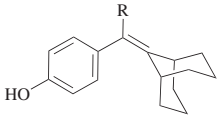
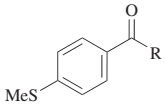
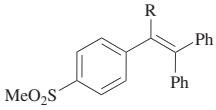
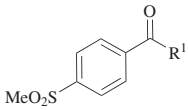
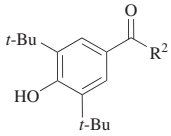
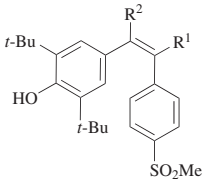
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{8-13}				
		$TiCl_4$, Zn		532
			R Me (—) 4-HOC_6H_4 (—)	
C_{8-22}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. Oxone, MeOH/THF/H_2O, rt, 15 h		533, 534
			R Me (62) Et (70) Bu (72) *n*-C_5H_{11} (—) *n*-C_6H_{13} (66) *n*-C_7H_{15} (68) *n*-C_9H_{19} (68) *n*-$C_{15}H_{31}$ (76)	
C_{8-14}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h		57
			R^1 / R^2 / (*E*)/(*Z*) Me / Ph (38) 27:73 Et / Ph (22) 0:100 Bu / Ph (25) 0:100 *n*-C_7H_{15} / Ph (27) 0:100 Ph / Me (30) 0:100 Ph / Et (35) 0:100 Ph / Bu (32) 0:100 Ph / *n*-C_7H_{15} (34) 0:100 Ph / *n*-$C_{15}H_{31}$ (37) 0:100	

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

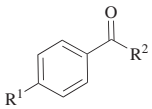
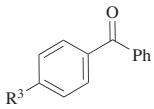
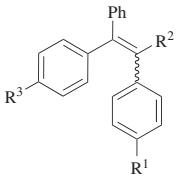
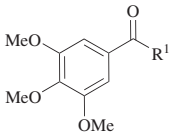
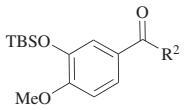
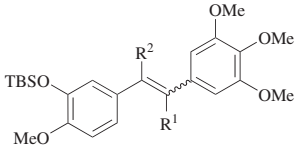
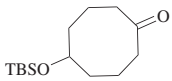
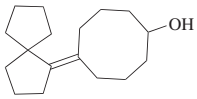
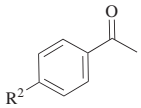
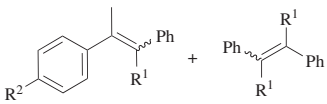
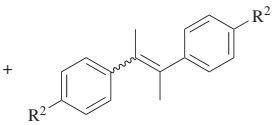
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{8-9}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h	 R^1 R^2 R^3 (*E*)/(*Z*) MeS Me Me (65) >35:65 MeO_2S Me Me (64) >34:66 MeS Et Me (60) >40:60 MeO_2S Et HO (75) <1:99	58
C_{8-13}				
		1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 5 h	 R^1 R^2 Me Ph (72) Et Ph (68) Ph Me (41) Ph Et (66) Ph Ph (31)	535
C_8				
		1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 3 h 3. HF	 (45)	412
C_{8-13}				
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux	 **I** **II** +  **III** R^1 R^2 **I** **II** **III** Me Me (41) (28) (29) Me HO (58) (18) (15) Me MeO (62.2) (12) (12.5) Me H_2N (60.2) (16) (13) Me (76.7) (9) (6) Ph H (65) (12) (13) Ph HO (71) (13) (7) Ph MeO (92) (4) (2) Ph H_2N (80) (12) (5) Ph (94) (3) (1.4)	144

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

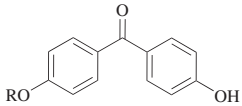
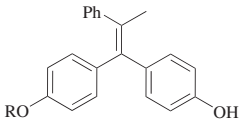
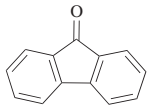
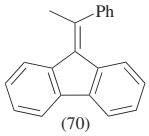
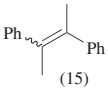
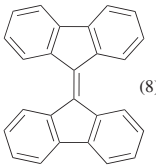
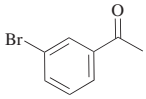
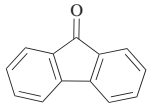
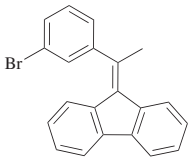
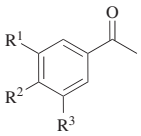
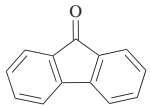
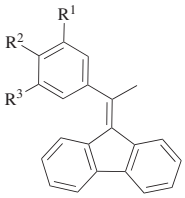
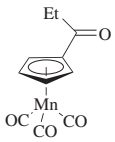
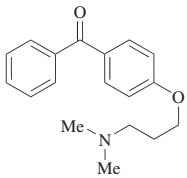
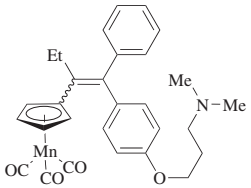
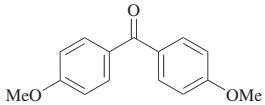
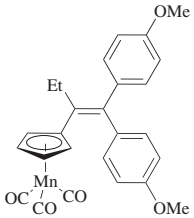
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 h	 R: H (78); $Me_2N(CH_2)_2$ (46)	536
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (70) +  (15) +  (8)	27
		1. $TiCl_3$, Mg, THF, reflux, 3.3 h 2. Reflux, 2.5 h	 (6)	537
C_{8-11}				
		1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. rt, 3.5 h	 R^1 R^2 R^3: H H H (25); H Br H (6); MeO H H (26); Me H H (22); Me Me H (17); Me Me Me (17); CF_3 H H (23)	537
C_8				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 1 h	 (54)	538
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 (83)	539

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

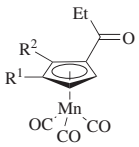
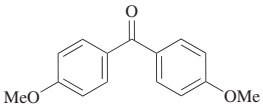
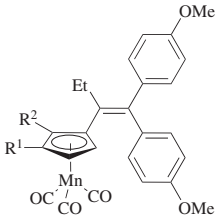
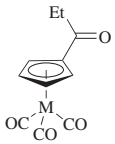
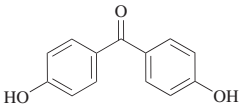
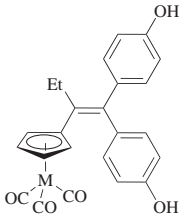
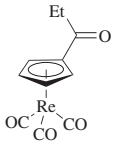
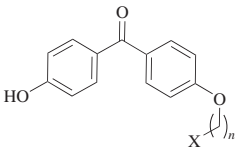
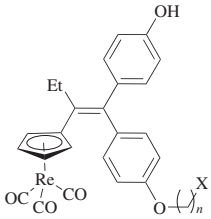
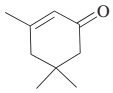
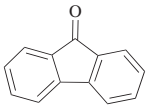
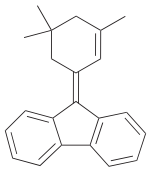
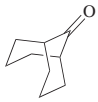
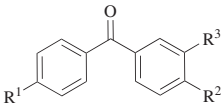
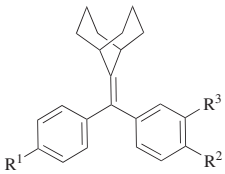
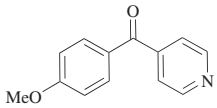
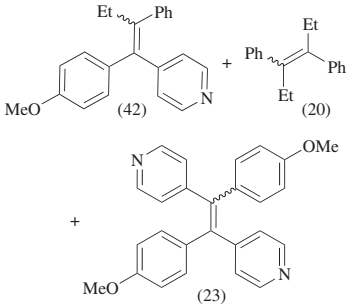
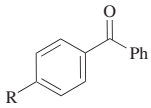
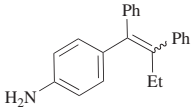
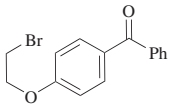
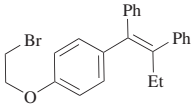
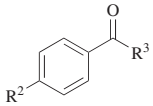
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{8-9}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 R^1 R^2 H H (83) H Me (64) Me H (48)	540
C_8				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 M Mn (96) Re (86)	541
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 *n* X 2 Br (64) 3 Br (>60) 4 Br (>60) 5 Br (>60) 8 Cl (>60)	542, 543
C_9				
		1. $TiCl_4$, Mg, THF, rt, 20 h 2. 0° to rt, 36 h	 (40)	544
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux, 1.5 h	 R^1 R^2 R^3 HO H H (82) HO F H (67) HO HO H (78) MeO H MeO (61) MeO MeO MeO (67)	529

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

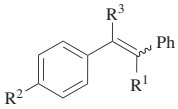
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, dioxane 2. Reflux, 4 h	 (42) + (20)	545
		1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, time		546
		$TiCl_4$, Zn, THF, reflux, 8 h	 (—)	547

R	Time		dr
H_2N	3 d	(38)	85:15
O_2N	4 h	(55)	85:15

C_{9-17}

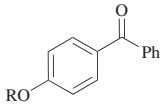


1. $TiCl_4$, Zn, THF, reflux, time 1
2. Reflux, time 2

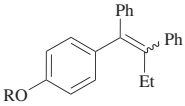


R^1	R^2	R^3	Time 1 (h)	Time 2 (h)		(*E*)/(*Z*)	
Et	BnO	Ph	1.5	0.5	(86.9)	1:5	55
Np	MeO_2S	n-C_5H_{11}	2	2.5	(68)	>39:61	58

C_9

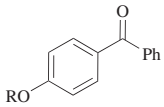


1. $TiCl_3$, Li, DME, reflux, 1 h
2. 18°, 2 h; then reflux, 12–20 h

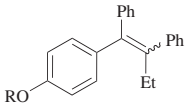


142

R		(*E*)/(*Z*)
H	(93)	1:9
Me	(76)	3:8
$Cl(CH_2)_2$	(68)	1:4
$Br(CH_2)_2$	(—)	1:4
$Me_2N(CH_2)_2$	(88)	1:3



1. $TiCl_4$, Zn, THF, reflux, 1–2 h
2. Reflux, 2–4 h



142

R		(*E*)/(*Z*)
H	(98)	1:7
$Cl(CH_2)_2$	(55)	0:100

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

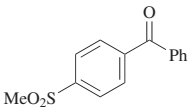
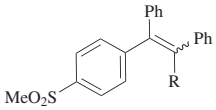
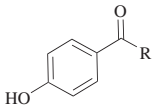
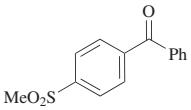
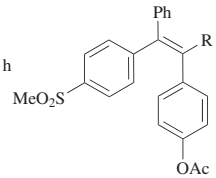
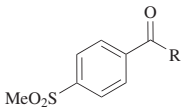
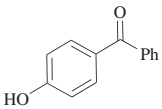
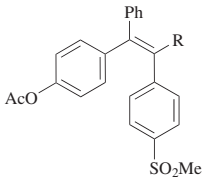
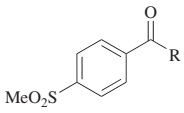
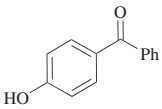
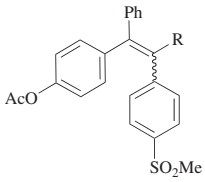
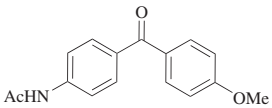
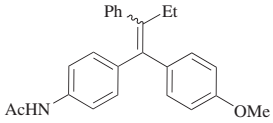
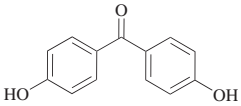
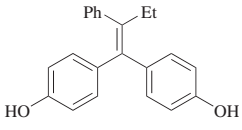
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{9-15}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h	 R: Et (62); Pr (—); Bu (—); n-C_6H_{13} (—); n-C_8H_{17} (—)	59
C_{9-11}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. AcCl, Et_3N, ether, rt, 1.5 h	 R: Et (62); Bu (67)	59
C_{9-22}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. AcCl, Et_3N, ether, rt, 15 h	 R: Et (72); Bu (68); n-C_7H_{15} (67); n-$C_{15}H_{31}$ (70)	534
C_{9-16}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. AcCl, Et_3N, ether, rt, 15 h	 R: Et (72) <1:99; Pr (68) <1:99; n-C_5H_{11} (70) <1:99; n-C_6H_{13} (70) <1:99; n-C_9H_{19} (63) <1:99	58
C_9				
		$TiCl_3$, $LiAlH_4$, THF, rt, 20 h	 (40), (E)/(Z) = 2:1	54
		$TiCl_4$, Zn, THF, reflux	 (73)	548

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

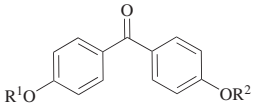
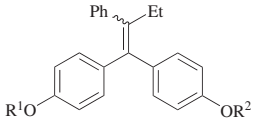
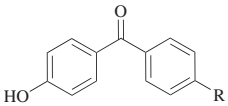
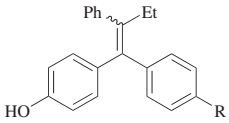
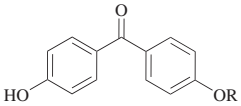
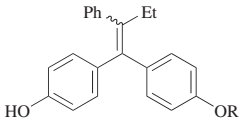
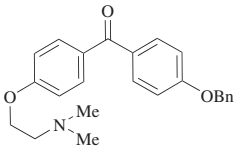
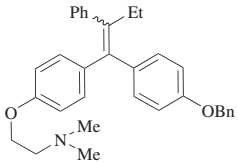
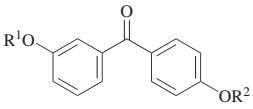
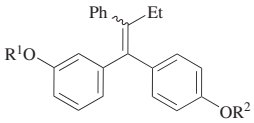
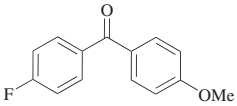
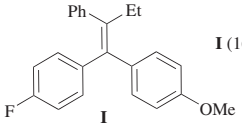
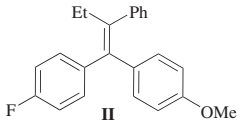
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux in the dark, 2.5 h	 R^1 / R^2 / (*E*)/(*Z*) / dr Bn / H / (72) / 4:1 / — 2,3,5,6-F_4-4-CF_3C_6 / Bn / (60) / — / 2:1	53
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 4 h	 R / (%) H / (95) PivO / (69)	549
		$TiCl_4$, Zn, THF	 R / (*E*)/(*Z*) *t*-BuCO / (—) / 14:1 BnO_2C / (—) / (—) Bn / (—) / (—) Ph_3C / (—) / (—)	52
		1. $TiCl_4$, Zn, THF, 60°, 2 h 2. 65°, 4 d	 (52)	550
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 5 h	 R^1 / R^2 / (%) / (*E*)/(*Z*) Piv / H / (65) / 100:1 H / $Et_2N(CH_2)_2$ / (60) / 2:1	56
		$TiCl_3$, $LiAlH_4$, THF, reflux, 4 h	 **I** +  **II** **I** (16), **I + II** (39)	54

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

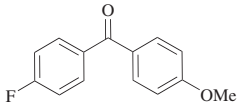
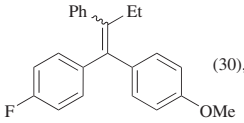
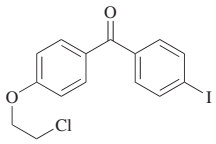
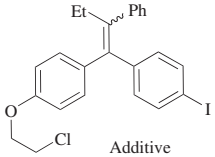
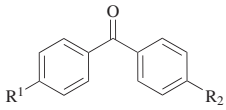
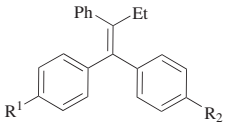
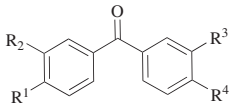
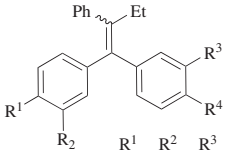
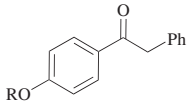
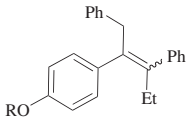
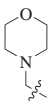
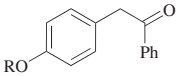
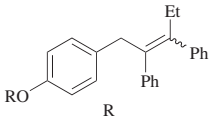
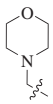
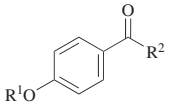
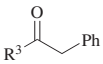
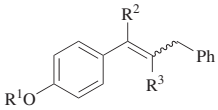
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, ether 2. rt, 16 h; then reflux, 4 h	 (30), (*E*)/(*Z*) = 3:1	54
		1. $TiCl_4$, Zn, dioxane, additive, reflux, 2 h 2. Reflux, 2.5 h	 Additive (*E*)/(*Z*) none (56.5) 3.9:1 dppe (63) 4.1:1	51
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 4 h	 R^1 R^2 HO BnO (—) HO $Br(CH_2)_2O$ (40) Br HO (70) MeO Me (55)	551
		$TiCl_4$, Zn, THF	 R^1 R^2 R^3 R^4 HO H BnO H (71) H HO H BnO (<61)	552
		$TiCl_4$, Zn, reflux, 4 h	 R (*E*)/(*Z*) Me_2NCH_2 (49.0) 1:4 Et_2NCH_2 (41.9) 5:6 (74.8) 1:2 (80.3) 1:2  (40.5) 1:2	554

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		$TiCl_4$, Zn, reflux, 4 h		554

R		(*E*)/(*Z*)
Me_2NCH_2	(71.2)	6:5
Et_2NCH_2	(40.2)	9:1
	(18.9)	6:5
	(38.4)	6:1
	(29.2)	3:1

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		$TiCl_4$, Zn, reflux, 4 h		554

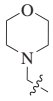
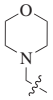
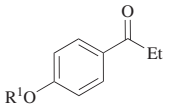
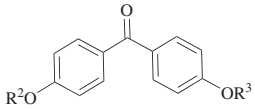
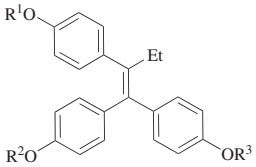
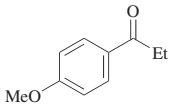
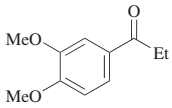
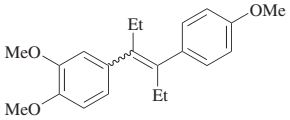
R^1	R^2	R^3		(*E*)/(*Z*)
Me_2NCH_2	Et	Ph	(44.3)	0:>100
Et_2NCH_2	Et	Ph	(34.7)	0:>100
	Et	Ph	(24.7)	1:5
	Et	Ph	(39.2)	1:5
	Et	Ph	(29.2)	1:5
Me_2NCH_2	Ph	Et	(69.0)	1:2
Et_2NCH_2	Ph	Et	(71.5)	1:2
	Ph	Et	(68.4)	1:2
	Ph	Et	(65.1)	1:2
	Ph	Et	(67.9)	1:2

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, THF, reflux, time 1 2. Reflux, time 2	 R^1 R^2 R^3 Time 1 (h) Time 2 (h) H H H 2 3 (51) Me Me 1.5 4 (60)	536 555
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (55)	556

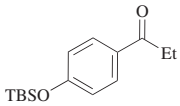
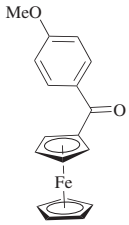
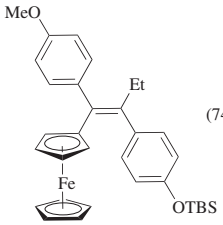
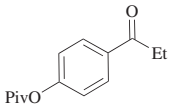
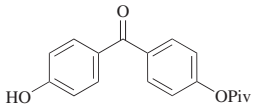
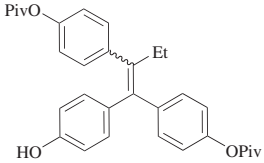
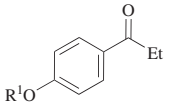
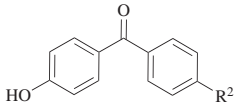
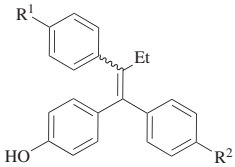
C_9				
		$TiCl_4$, Zn, THF, reflux	 (74), (*E*)/(*Z*) = 7:93	548
		$TiCl_4$, Zn, THF, reflux, 4 h	 (67)	557
		1. TiCl4, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 R^1 R^2 dr Piv H (70) 1:1 Piv PivO (67) 1:5 TBS TBSO (75) 1:1	558

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

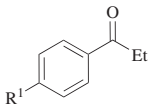
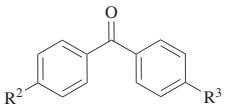
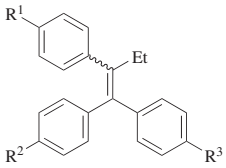
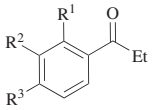
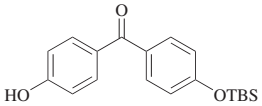
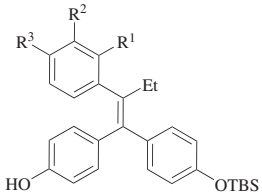
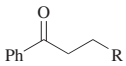
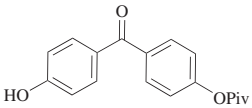
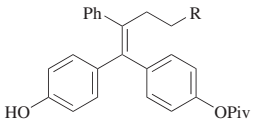
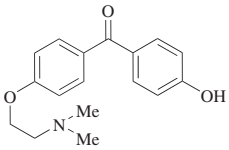
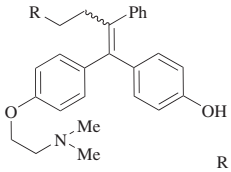
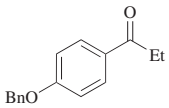
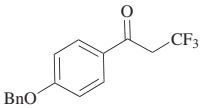
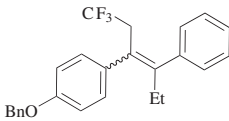
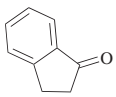
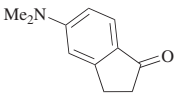
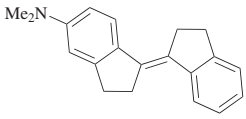
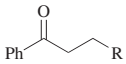
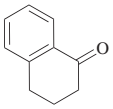
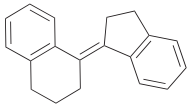
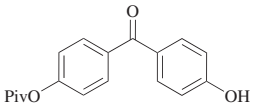
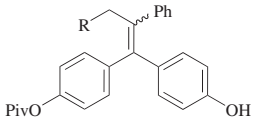
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 12 h	 R^1 R^2 R^3 (*E*)/(*Z*) H HO H (84) 1:1 H HO HO (39) 1:1 HO H H (83) 1:1	559
		1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 4 h	 R^1 R^2 R^3 H H TBSO (87) PivO H H (41) H PivO H (49) H H PivO (67) MeO H H (21) H MeO H (29) H H MeO (54)	555
C_9				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 5 h	 R (*E*)/(*Z*) H (82) >100:1 Cl (47) >100:1	560
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 5 h	 R (*E*)/(*Z*) H (57) 32:1 Cl (63) 16:1	560
		$TiCl_3$, Zn/Cu, THF	 (40–60)	425
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 (—)	561

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9				
		1. $TiCl_4$, Zn, THF 2. Reflux, 18 h	 (8)	187
C_{10-12}				
		$TiCl_4$, Zn, THF, heat		553

R	
$Cl(CH_2)_2$	(—)
$Cl(CH_2)_3$	(—)
$Cl(CH_2)_4$	(—)
$MeO_2C(CH_2)_2$	(—)
$MeO_2C(CH_2)_3$	(—)
$MeO_2C(CH_2)_4$	(—)

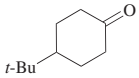
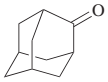
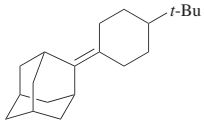
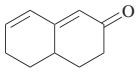
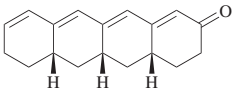
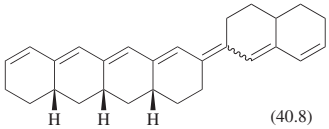
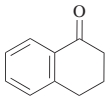
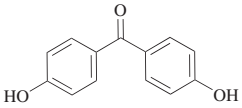
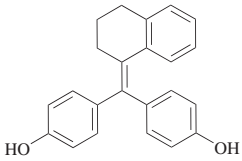
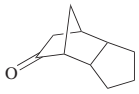
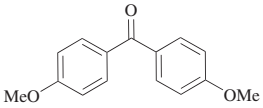
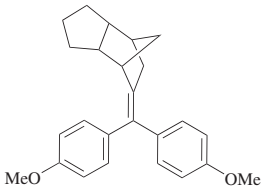
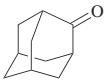
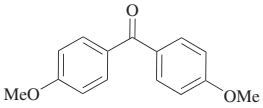
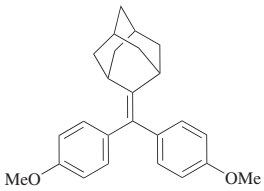
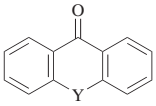
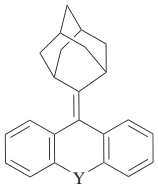
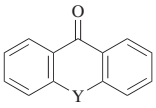
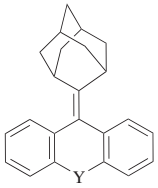
C_{10}				
		1. $TiCl_3$, $LiAlH_4$, THF, reflux, 15 min 2. Reflux, 4 h	 (27.5)	562
		1. $TiCl_4$, Zn, THF, –15° to reflux; then py, reflux, 15 min 2. Reflux, 15 min	 (40.8)	204
		Ti(0), THF, reflux	 (46)	563

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

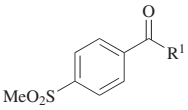
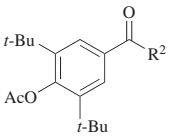
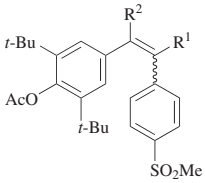
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}				
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux, 1.5 h	 (64)	529
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux, 1.5 h	 (54)	529
		$TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 40 h		

Y		
PhN, BnN, CH_2, nil	(30–79)	564
EtO_2CCH_2N	(63)	565

		1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 1 h 2. Reflux, 30 min; then addition of ketones; then reflux, 5 h		566

Y	
—	(29)
MeN	(74)
EtO_2CCH_2N	(63)
PhN	(51)
BnN	(76)
CH_2	(64)

C_{11-14}

		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h		57

R^1	R^2		(*E*)/(*Z*)
Ph	Bu	(57)	6:94
Bu	Ph	(55)	0:100
Ph	n-C_7H_{15}	(57)	17:83
n-C_7H_{15}	Ph	(45)	22:78

C_{11}

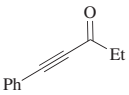
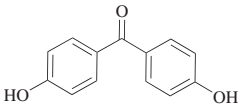
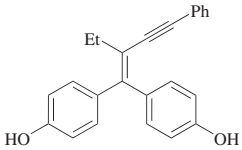
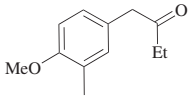
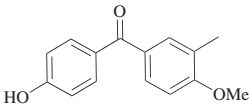
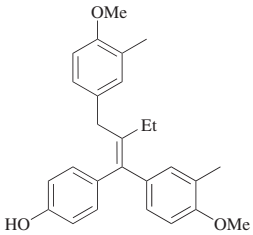
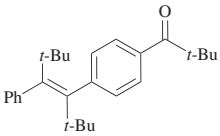
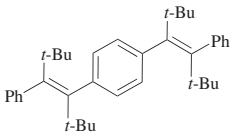
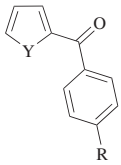
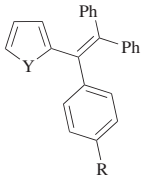
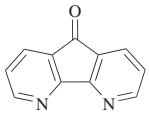
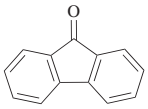
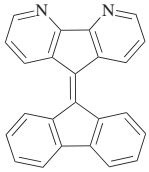
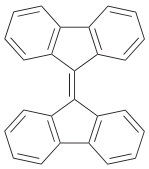
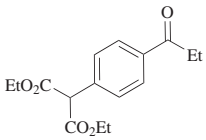
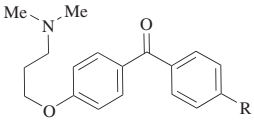
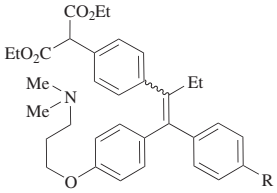
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 (71.7)	567

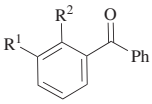
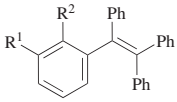
TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}				
		1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 4 h	 (70)	555
		$TiCl_4$, Zn, THF	 (—)	499
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux		568

R	Y	
F	O	(70)
	S	(65)

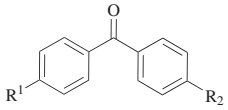
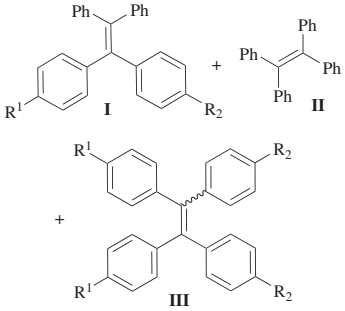
		$TiCl_3$, $LiAlH_4$, THF, reflux, 12 h	 (4) +  (14)	213
C_{12}				
		$TiCl_4$, Zn, THF, heat, 3 h		569

R		(*E*)/(*Z*)
H	(85)	0:100
HO	(55)	20:80

C_{13}				
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux		568

R^1	R^2	
H	HO	(64)
H	H_2N	(72)
H		(61)
HO	H	(62)

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux, time		144

R^1	R^2	Time (h)	**I**	**II**	**III**
H	Me	6	(44)	(28)	(28)
Me	Br	5	(39)	(30)	(30)
Me	Me	34	(73)	(13)	(8)
H		16	(62)	(16)	(13)
H		36	(53)	(20)	(16)
H		38	(52)	(21)	(15)
		36	(65)	(15)	(11)
H	HO	32	(66)	(14)	(10)
HO	HO	36	(69)	(14)	(10)
H	MeO	—	(62)	(16)	(12)
MeO	MeO	34	(59)	(17)	(13)
H	$HO(CH_2)_2O$	30	(60)	(17)	(14)
$HO(CH_2)_2O(CH_2)_2O$	$HO(CH_2)_2O(CH_2)_2O$	38	(89)	(4)	(3)
H	H_2N	13	(80)	(10)	(7)
H	$PhHNCH_2$	15	(68)	(12)	(9)

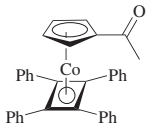
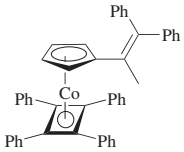
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 2 h 2. Reflux, 12 h		(71)	570

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

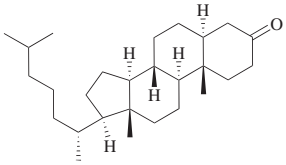
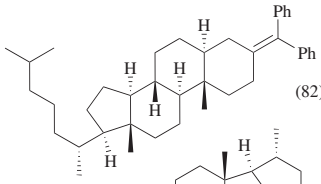
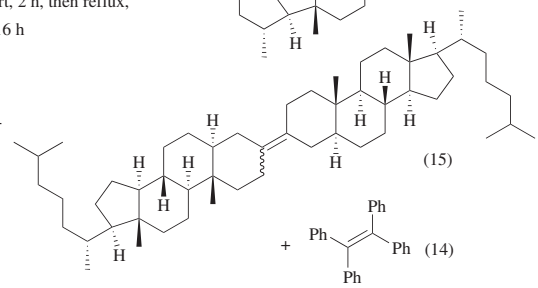
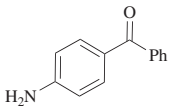
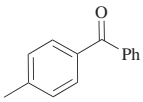
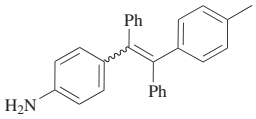
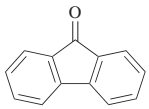
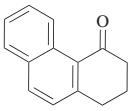
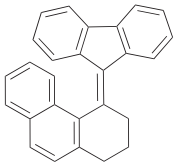
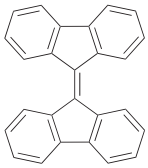
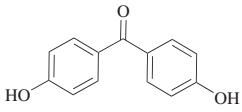
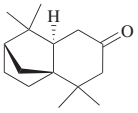
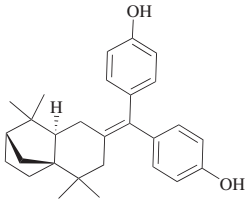
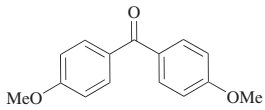
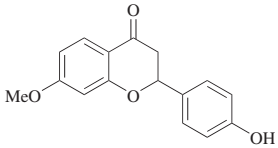
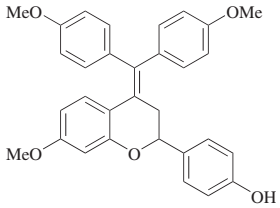
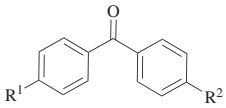
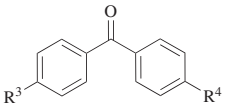
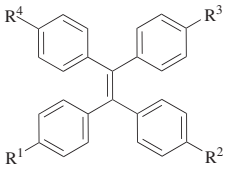
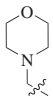
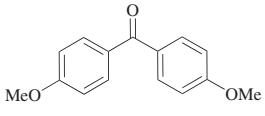
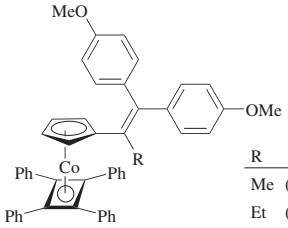
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h, then reflux, 16 h	 (82) +  (15) + (14)	27
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux	 (76)	144
		$TiCl_3$, $LiAlH_4$, THF	 (25) +  (35)	516
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Reflux, 1.5 h	 (67)[a]	529
		1. $TiCl_4$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 3 h	 (35) + self-coupling products	571

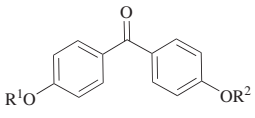
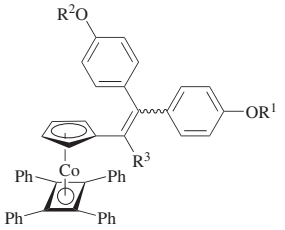
TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		1. $TiCl_4$, Zn, THF, reflux, 2.5 h 2. Py, reflux		568

R^1	R^2	R^3	R^4	
H	H	H	HO	(66)
H	H	HO	HO	(69)
H	H	MeO	MeO	(59)
H	H	H	H_2N	(80)
HO	HO	H	Br	(69)
H	H	H	Me	(44)
H	H	H		(62)
H	H	H		(61)
H	H			(73)
H	Br			(77)

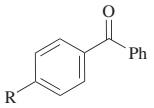
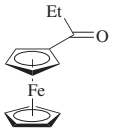
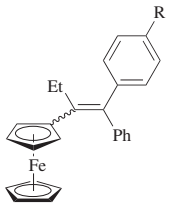
		1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 2.5 h 2. Reflux, overnight		550

R	
Me	(12)
Et	(13)

		1. $TiCl_4$, Zn, THF, 60°, 2 h 2. Temp, time		550

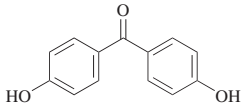
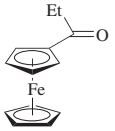
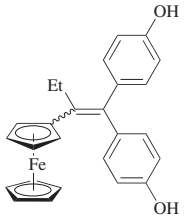
R^1	R^2	R^3	Temp (°)	Time (d)	
H	H	Me	50	4	(90)
H	H	Et	50	4	(26)
Bn	Bn	Me	65	2	(40)
Bn	Bn	Et	50	4	(20)
H	$Me_2N(CH_2)_2$	Me	50	4	(9)

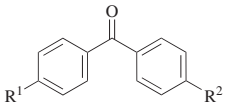
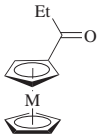
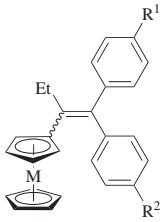
TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-14}				
		1. $TiCl_4$, Zn, THF, reflux, time 1 2. Reflux, time 2		

R	Time 1 (h)	Time 2 (h)		(*E*)/(*Z*)	dr	Refs.
Cl	1.5	4	(58)	50:50	—	572
Br	1.5	4	(13)	36:64	—	572
CF_3	1.5	4	(22)	55:45	—	572
H_2N	1.5	4	(54)	—	55:45	546
MeO	2.5	15	(66)	—	—	573

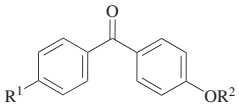
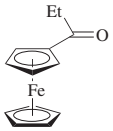
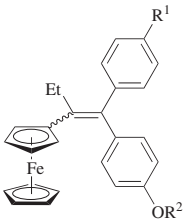
C_{13}

		1. $TiCl_4$, Zn, THF, 60°, 2 h 2. 65°, 2 d	 (56)	550

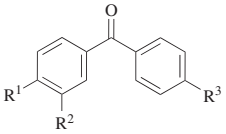
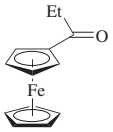
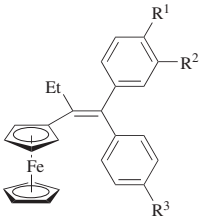
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, time		

M	R^1	R^2	Time (h)		Refs.
Fe	HO	HO	1.5	(52.5)	574
Fe	MeO	MeO	5	(86)	575
Fe	MeS	MeS	5	(30)	575
Fe	*t*-BuS	*t*-BuS	5	(25)	575
Ru	HO	HO	2	(96)	541
Ru	HO	$Br(CH_2)_2O$	2	(76)	576
Ru	HO	$Br(CH_2)_3O$	2	(91)	576
Ru	HO	$Br(CH_2)_4O$	2	(83)	576
Ru	HO	$Br(CH_2)_5O$	2	(94)	576

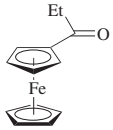
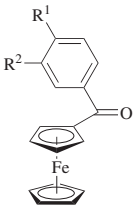
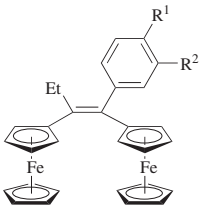
TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		$TiCl_4$, Zn, THF, reflux		

R^1	R^2		Refs.
H	H	(—)	577
HO	H	(53)	548, 574
HO	$Br(CH_2)_5$	(50.7)	577
HO	$Cl(CH_2)_8$	(46.5)	577
H	$Br(CH_2)_5$	(50)	577
H	$Cl(CH_2)_8$	(39)	577

		1. $TiCl_4$, Zn, THF, reflux, time 2. Reflux, 2 h		

R^1	R^2	R^3	Time (h)		Refs.
H	H	HO	1.5	(36)	578
HO	H	$Br(CH_2)_2O$	1.5	(46)	578
H	H	H	2	(25)	579
H	HO	H	2	(19)	579
H	HO	HO	2	(58)	579

		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h		

R^1	R^2		Refs.
HO	H	(39)	579
H	HO	(39)	

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

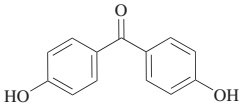
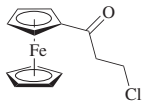
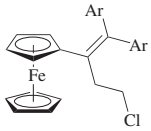
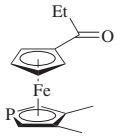
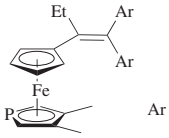
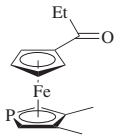
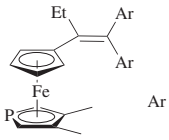
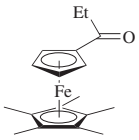
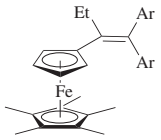
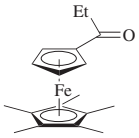
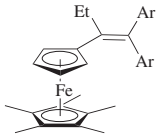
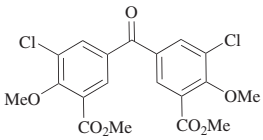
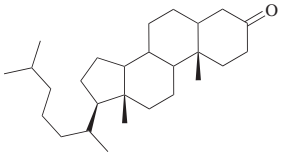
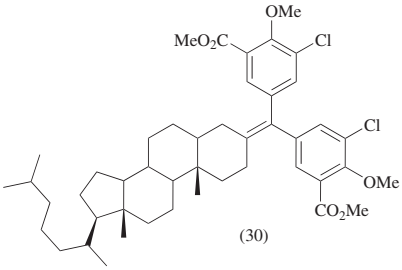
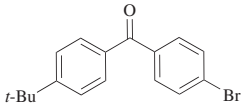
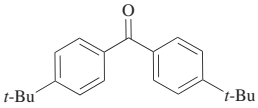
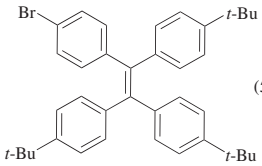
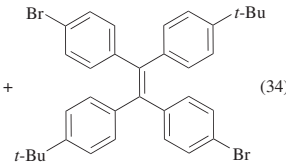
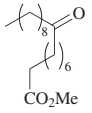
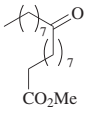
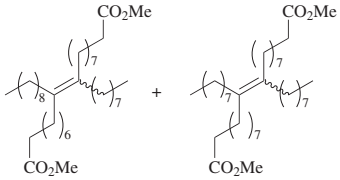
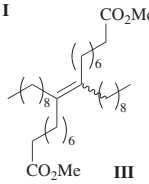
Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}				
		1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Heat, 2 h	 (47) Ar = 4-HOC_6H_4	541
		$TiCl_4$, Zn	 (16) Ar = 4-HOC_6H_4	580
		1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 2 h	 (16) Ar = 4-HOC_6H_4	541
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Heat, 2 h	 (19) Ar = 4-HOC_6H_4	541
		$TiCl_4$, Zn	 (14) Ar = 4-HOC_6H_4	580
C_{15}				
		1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 5.5 h	 (30)	581
C_{17}				
		$TiCl_4$, Zn, THF, 60°, 1 h	 (58)	582
			 (34)	

TABLE 2B. MIXED-COUPLING OF KETONES (*Continued*)

Ketone 1	Ketone 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}				
		1. $TiCl_4$, Zn, THF, rt, 10 min 2. Reflux, overnight	 **I** + **II**	494
			+  **I + II + III** (83)	
			III	

[a] Optically active starting material was employed.

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES

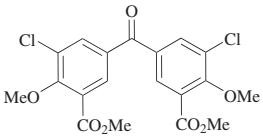
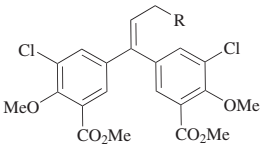
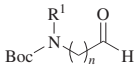
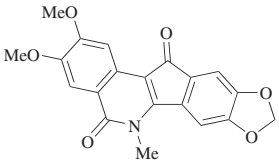
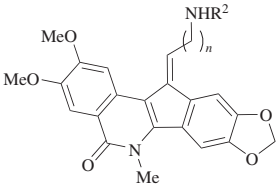
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{2-3}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 2 h 2. Reflux, time	 R / Time (h): BocHN 3 (23); $FmocHNCH_2$ 2.5 (72)	583
C_{2-6}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h 3. 4 N HCl, rt, overnight	 n / R^1 / R^2: 1 / H / H (30); 1 / $BocHN(CH_2)_3$ / $H_2N(CH_2)_3$ (24); 2 / Me / Me (48); 2 / $BocHN(CH_2)_3$ / $H_2N(CH_2)_3$ (36); 3 / Me / Me (48); 3 / Boc / H (35); 4 / Boc / H (20); 5 / H / H (45)	584

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

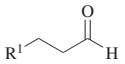
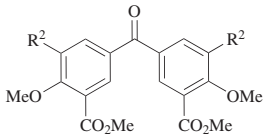
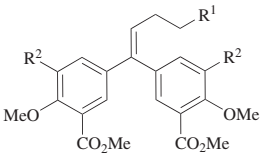
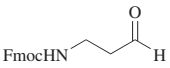
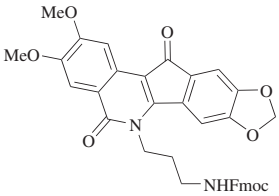
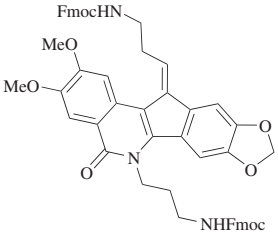
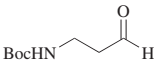
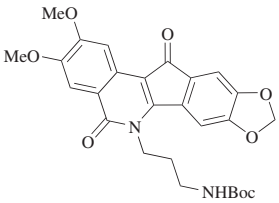
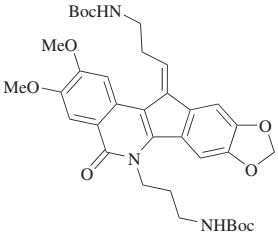
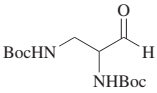
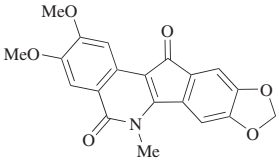
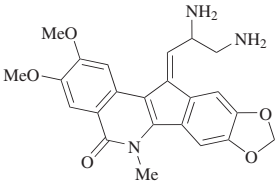
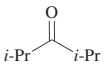
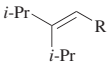
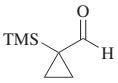
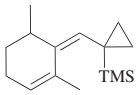
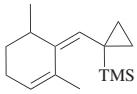
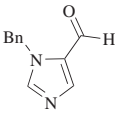
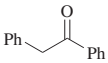
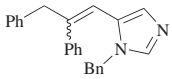
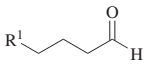
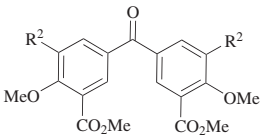
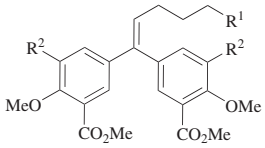
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_3				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 1 h 2. Reflux, 14 h	 R^1 / R^2: MeO_2CHN / Cl (32); MeO_2CHN / Me (38.8); MeO_2CHN / Br (38.1); EtO_2CHN / Cl (33.3); EtO_2CHN / Me (41.5); *i*-BuO_2CHN / Cl (39.8); *i*-BuO_2CHN / Me (32); / Cl (32); / Br (51)	585
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h	 (63)	586
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h 3. K_2CO_3, Boc_2O, rt, 12 h	 (39)	586
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h 3. 4 N HCl, rt, overnight	 (45)	584

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{4\text{-}7}$				
		—	 R: *i*-Pr (7); Ph (10)	527
		$TiCl_3$, Li (or Zn/Cu), DME, heat	 (30–60)	587
		1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. rt, 3 h; then reflux, 30 h	 (60)	143
		1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 3 h	 (—)	588

$C_{4\text{–}10}$

		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 1–3 h 2. Reflux, time		585

Continued on next page.

R^1	R^2	Time (h)	
Et	F	0.5	(66)
Et	Me	0.5	(87)
Et	CF_3	1	(52)
ethynyl	Cl	1.5	(25)
ethynyl	Br	2	(27)
CH_2=CH	Cl	1.5	(16)
CH_2=CH	Br	1.5	(52.5)
Ph	Cl	2	(58.22)
Ph	Br	2	(64)
MeO_2C	F	0.75	(46)
MeO_2C	Me	0.75	(49)
MeO_2C	CF_3	1	(48)
EtO_2C	Cl	3	(40.8)
EtO_2C	Me	14	(20.8)
EtO_2C	Br	20	(22)
PrO_2C	Cl	14	(40.5)
PrO_2C	Me	14	(48.8)
PrO_2C	Br	16	(20.4)
i-PrO_2C	Cl	14	(38.5)
i-PrO_2C	Me	14	(26.9)

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

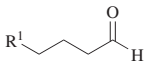
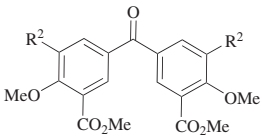
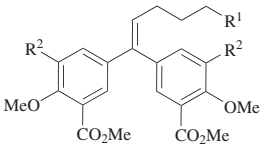
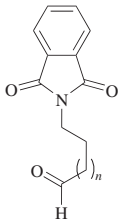
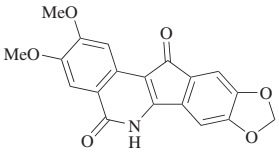
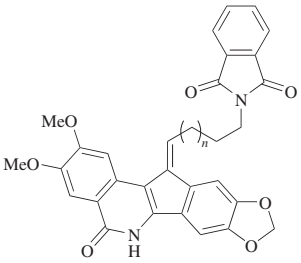
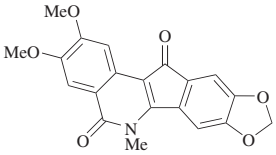
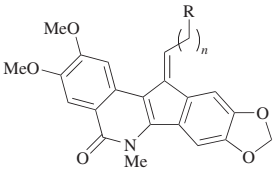
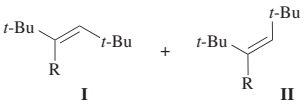
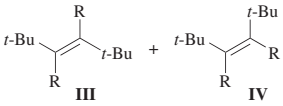
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{4-10}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 1–3 h 2. Reflux, time	 R^1 / R^2 / Time (h) *i*-PrO_2C / Br / 20 (33.6) Me_2NCO / Cl / 14 (40) Me_2NCO / Me / 5 (17.4) (1-piperidyl)CO / Cl / 14 (40.5) (1-piperidyl)CO / Me / 14 (31) $TMS(CH_2)_2OCO$ / Me / 14 (28) TMS / Cl / 1.5 (73) MeSCO / Cl / 14 (30) EtSCO / Cl / 14 (20)	585
C_{4-5}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h 3. 4 N HCl, rt, overnight	 *n* 1 (44) 2 (45)	584
C_{4-6}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 3-6 h 2. Reflux, 1-2.5 h	 *n* / R 3 / Cl (43) 3 / Br (30) 4 / Br (33) 5 / Br (21)	589
C_5				
		1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 66 h	 **I** + **II** R / **I** / **II** / **III** / **IV** Me (33.8) (17.5) (17.8) (17.3) Et (60.4) (23.7) (3.3) (0.2) +  **III** + **IV**	404

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

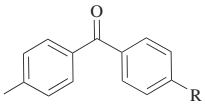
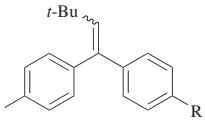
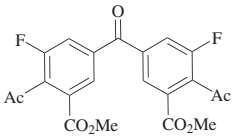
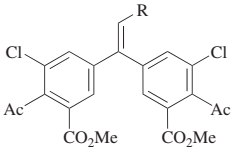
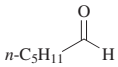
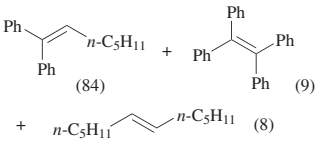
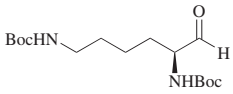
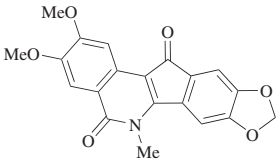
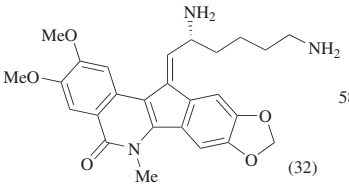
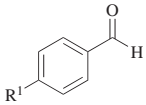
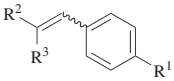
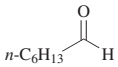
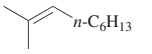
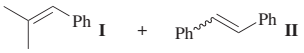
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5				
		1. $TiCl_4$, Zn, THF 2. Reflux, 2 h	 R / (*E*)/(*Z*) H_2N (9) 63:37 Me_2N (75) 77:23 HO (94) 70:30 MeO (95) 66:34 Br (89) 49:51	590
C_{5-6}				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 1 h 2. Reflux, time	 R / Time (min) $MeO_2C(CH_2)_3$ 45 (46) n-C_5H_{11} 30 (66)	591
C_6				
		1. $TiCl_3$, Li, DME, reflux, 1 h 2. rt, 2 h; then reflux, 16 h	 (84) (9) (8)	27
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 4 h 3. 4 N HCl, rt, overnight	 (32)	584
C_7				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h	 R^1 / R^2 / R^3 / (*E*)/(*Z*) MeS / 4-HOC_6H_4 / Ph (63) >49:51 MeO_2S / 4-BrC_6H_4 / Ph (64) >44:56 H / 4-$MeSC_6H_4$ / n-C_7H_{15} (61) >35:65 MeO_2S / Np / Ph (68) >47:53 MeO_2S / 4-HOC_6H_4 / Ph (67)[a] <10:90	58
		$W_2(OCH_2CMe_3)_6(py)_2$, 22°, 12–22 h	 (18)	99
		MCl_3, Zn, MeCN, reflux	 M / Time (h) / **I** / **II** Al 20 (78) (16) 88 In 12 (60) (40) 104	

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

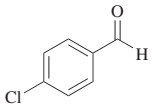
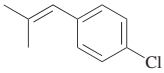
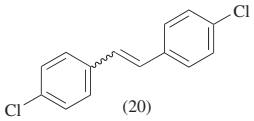
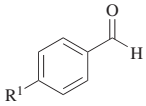
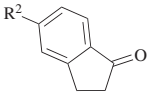
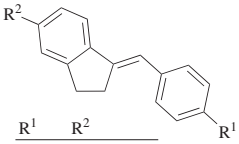
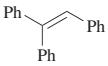
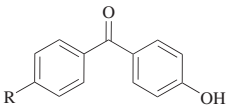
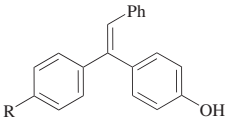
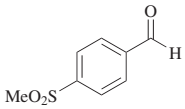
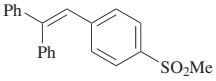
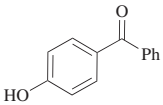
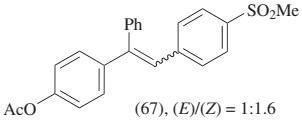
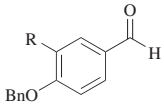
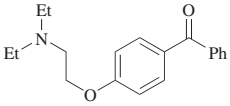
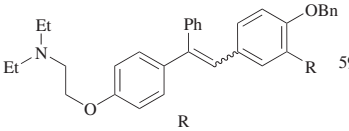
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$AlCl_3$, Zn, MeCN, reflux, 19 h	 (75) +  (20)	88
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 R^1 R^2 Me_2N H (—) H Me_2N (—)	561
		1. Aldehyde, {4-*t*-Bu-calix[4]-$(O)_4\}_2Nb_2Na_2(THF)_6$, THF, rt, overnight 2. Ketone, rt, 3 h	 (92)	592
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 4 h	 R H (30) BnO (34)	549
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h	 (70)	534
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h 3. AcCl, Et_3N, ether, rt, 1.5 h	 (67), (*E*)/(*Z*) = 1:1.6	534
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 2 h	 R H (49) MeO (36)	593

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

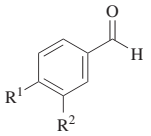
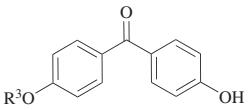
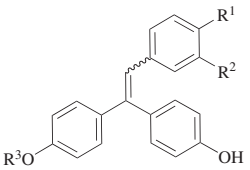
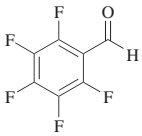
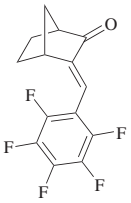
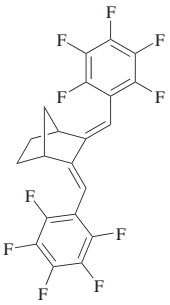
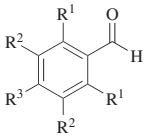
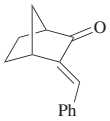
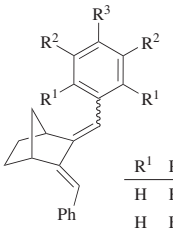
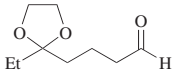
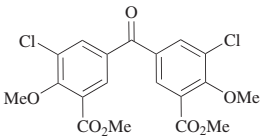
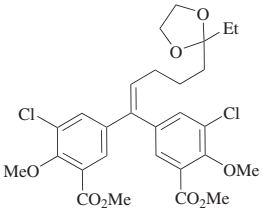
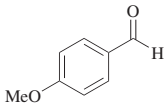
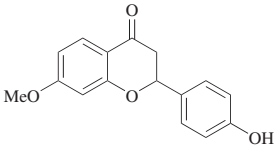
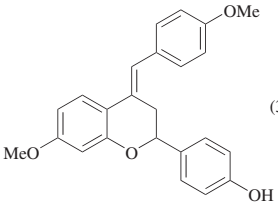
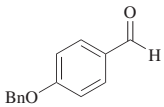
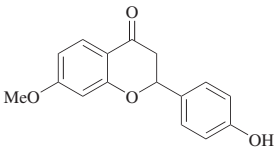
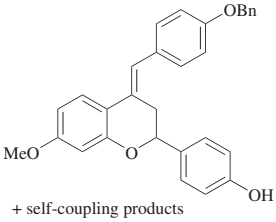
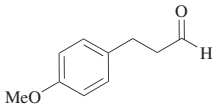
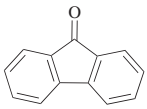
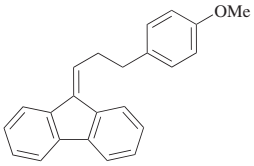
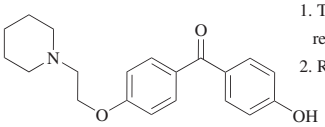
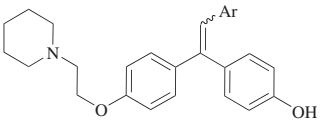
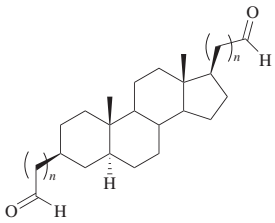
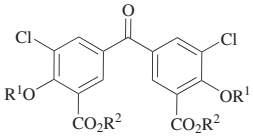
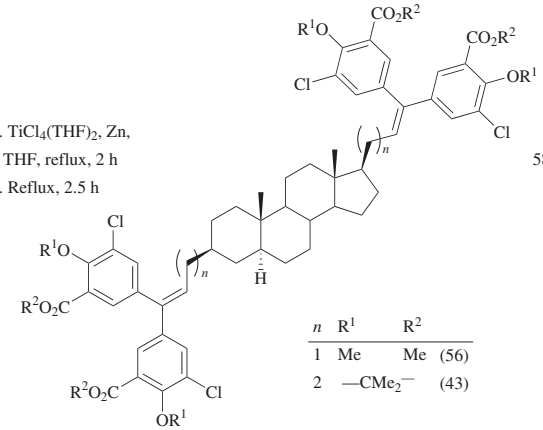
Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3 h	 R^1 R^2 R^3 (*E*)/(*Z*) MeO MeO $Me_2N(CH_2)_2$ (39) 1:1 MeO H $Me_2N(CH_2)_2$ (45) 1:1 HO H H (40) — HO MeO H (46) —	536
		$TiCl_4$, Zn, THF, reflux	 (—)	594
		$TiCl_4$, Zn, THF, reflux	 R^1 R^2 R^3 dr H H F (—) 95:5 H F H (—) — F F H (—) — F F F (30) —	595
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 2 h 2. Reflux, 1.5 h	 (77.5)	591
		1. $TiCl_4$, $LiAlH_4$, THF, reflux, 1 h 2. Reflux, 3 h	 (30) + self-coupling products	571

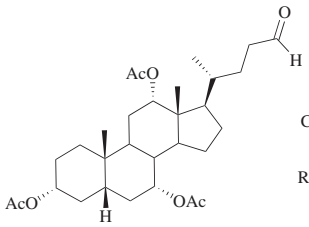
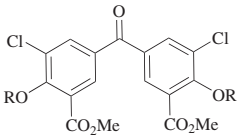
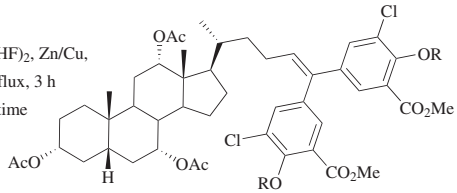
TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		$TiCl_4$, Zn, THF, reflux	 (20) + self-coupling products	571
C_9				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 4 h 2. Reflux, 3 h	 (94)	586
C_{11}				
		1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 3.2 h		596

Ar		(*E*)/(*Z*)
5-HO-1-Np	(60)	1:1.8
6-HO-1-Np	(66)	1:1
6-HO-2-Np	(35)	19:1

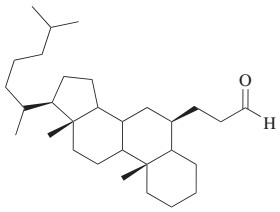
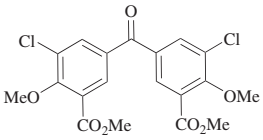
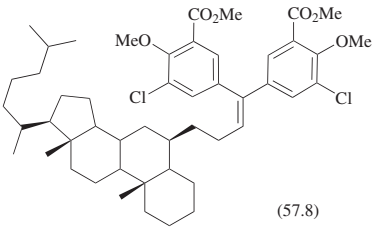
$C_{23–25}$				
		1. $TiCl_4(THF)_2$, Zn, THF, reflux, 2 h 2. Reflux, 2.5 h		583

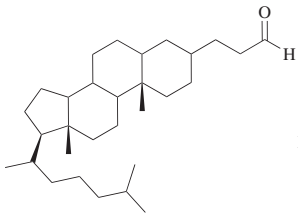
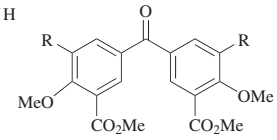
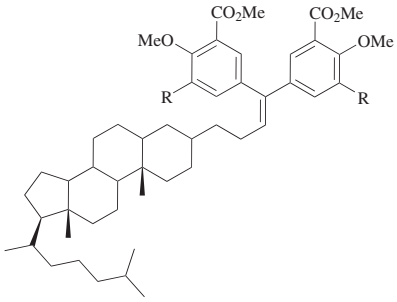
n	R^1	R^2	
1	Me	Me	(56)
2	—CMe_2—		(43)

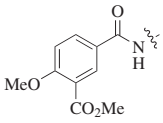
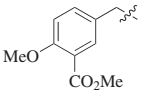
C_{24}				
		1. $TiCl_4(THF)_2$, Zn/Cu, DME, reflux, 3 h 2. Reflux, time		597

R	Time (h)	
Me	12	(25)
Ac	24	(25)

TABLE 2C. MIXED-COUPLING OF ALDEHYDES AND KETONES (*Continued*)

Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{30} 		1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 1.5 h 2. Reflux, 1 h	 (57.8)	598

Aldehyde	Ketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{30} 		1. $TiCl_4(THF)_2$, Zn, THF, reflux, time 2. Reflux, 1 h		599

R	Time (h)	
	0.5	(25)
	1	(33)

[a] The yield was obtained after acetylation of the hydroxyl group.

TABLE 2D. MIXED-COUPLING BETWEEN KETONES AND CARBOXYLIC ACID DERIVATIVES

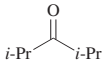
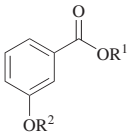
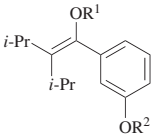
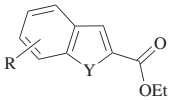
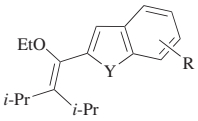
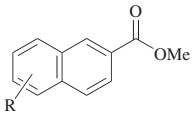
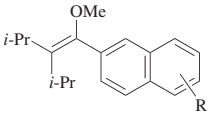
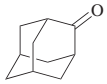
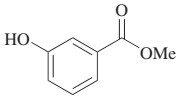
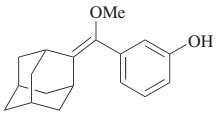
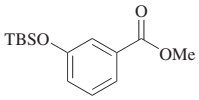
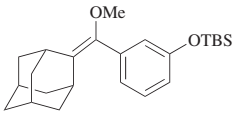
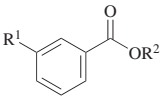
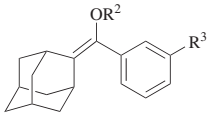
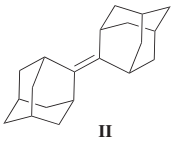
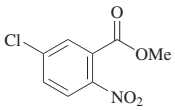
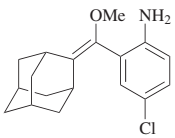
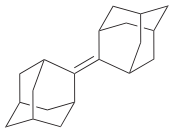
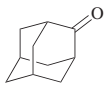
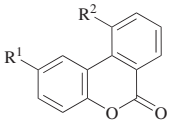
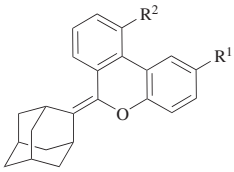
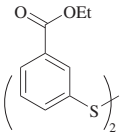
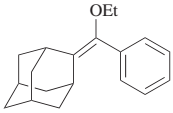
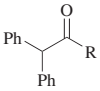
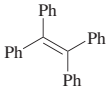
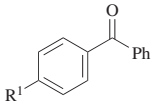
Ketone	Carboxylic Acid Derivative	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7				
		1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 15 min 2. Reflux, 20 min 3. Reflux, 30 min	 R^1 R^2 Me Me (42.2) Et Me (60) *i*-Pr Me (67) *t*-Bu Me (47) Me TBS (52)	135
		—	 R Y 5-MeO, 6-MeO, 7-MeO O, S (30–50)	600
		1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 30 min 2. Reflux, 30 min 3. Reflux, 1.5 h	 R 3-MeO (52.1) 4-MeO (44.2) 5-MeO (47.7) 6-MeO (47.7) 7-MeO (28.2) 8-MeO (34.9)	601
C_{10}				
		1. $TiCl_4$, $LiAlH_4$, Et_3N, THF, reflux, 1 h 2. Reflux, 45 min 3. Reflux, 1.5 h	 (27)	602
		1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 30 min 2. Reflux, ~25 min 3. Reflux, 5 h	 (48)	603
		$TiCl_3$, $LiAlH_4$, Et_3N, THF, 70°, 20 h	 +  **I** **II** R^1 R^2 R^3 **I** **II** TBSO Me TBSO (41–59) (—) Cl Me Cl (40) (22) F Et F (38) (19) Br Et H (38) (11) HS Et H (52) (—) *t*-BuS Et *t*-BuS (60) (—)	136
		$TiCl_3$, $LiAlH_4$, Et_3N, THF, 70°, 20 h	 +  (17) (35)	136

TABLE 2D. MIXED-COUPLING BETWEEN KETONES AND CARBOXYLIC ACID DERIVATIVES (*Continued*)

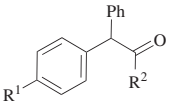
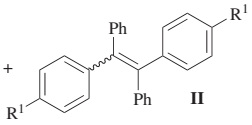
Ketone	Carboxylic Acid Derivative	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}				
		—	 R^1 R^2: H TBSO (~25); TBSO H (~25)	604
		$TiCl_3$, $LiAlH_4$, Et_3N, THF, 70°, 20 h	 (57)	136
C_{13}				
		$TiCl_4$, Zn; then 3% HCl	 **I** +  **II**	134

R	I	II
Me	(69.8)	(15.1)
Ph	(68.6)	(24.1)
4-$MeOC_6H_4$	(66.7)	(30.1)
4-ClC_6H_4	(52.2)	(27.1)
3-ClC_6H_4	(47.8)	(21.1)
3-MeC_6H_4	(60.6)	(18.1)

$C_{13–14}$



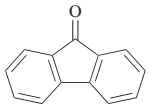
$TiCl_4$, Zn; then 3% HCl

 **I** +  **II**

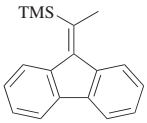
134

R^1	R^2	I	II
H	Ph	(46.6)	(30.1)
H	Bn	(49.0)	(18.1)
Cl	1-$NpCH_2$	(70.3)	(20.7)
H	1-$NpCH_2$	(66.7)	(24.0)
Me	1-$NpCH_2$	(48.6)	(29.6)
MeO	1-$NpCH_2$	(44.4)	(25.5)

C_{13}

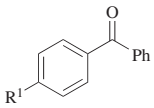
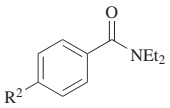
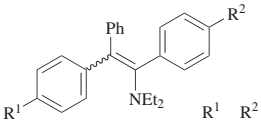


Ketone, Yb, THF, rt, 3 d; then acylsilane, rt, 1 d

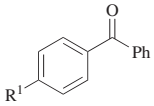
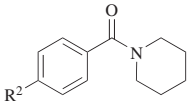
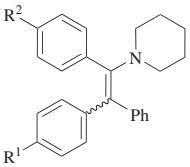
 (36)

132

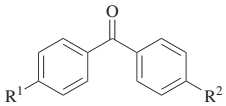
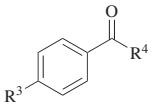
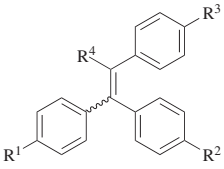
TABLE 2D. MIXED-COUPLING BETWEEN KETONES AND CARBOXYLIC ACID DERIVATIVES (*Continued*)

Ketone	Carboxylic Acid Derivative	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-19} 		SmI_2, Mg, THF, 67°		107

R^1	R^2	Time (h)	
H	H	6	(65)
Cl	H	6	(57)
Me	H	6	(60)
Ph	H	6	(63)
H	Cl	7	(63)
H	MeO	6	(65)

C_{13-14} 		SmI_2, Mg, THF, 67°		107

R^1	R^2	Time (h)	
H	Cl	6	(67)
Me	H	5	(68)

C_{13-19} 		SmI_2, Mg, THF, 67°		106

R^1	R^2	R^3	R^4	Time (h)	
H	H	H	Et_2N	3	(80)
H	Me	H	Et_2N	3	(78)
Me	Me	H	Et_2N	3	(76)
H	Cl	H	Et_2N	4	(68)
H	Ph	H	Et_2N	3	(81)
H	Me	H		3	(83)
H	H	MeO	Et_2N	3	(75)
H	Me	MeO	Et_2N	3	(73)
Me	Me	MeO	Et_2N	3	(67)
H	Ph	MeO	Et_2N	3	(75)
H	H	Cl	Et_2N	4	(67)
H	Me	Cl	Et_2N	4	(65)
H	H	Cl		4	(63)

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES

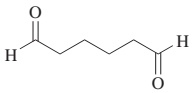
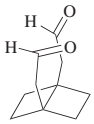
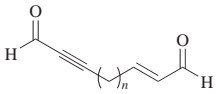
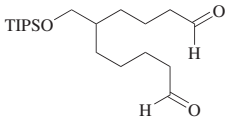
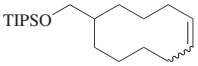
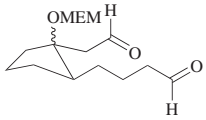
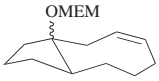
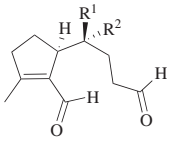
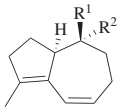
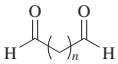
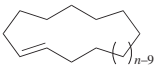
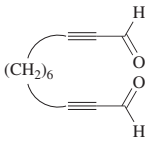
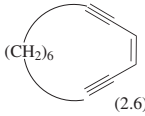
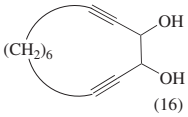
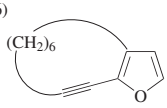
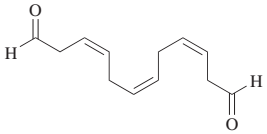
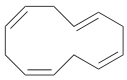
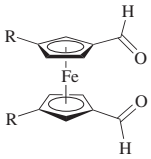
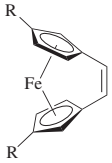
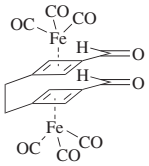
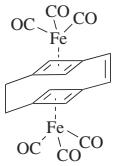
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h 3. Reflux, 14 h	(96)[a]	73, 74
C_{10} 	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 1.5 h 2. Reflux, 4 h 3. Reflux, overnight	(9.3)	605
$C_{10–14}$ 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. rt, 30 h 3. rt	n: 4 (5); 5 (38); 6 (16); 7 (37); 8 (44)	227
C_{11} 	$TiCl_3$, Zn/Cu, DME, reflux	 (86), (*E*)/(*Z*) = 1.7:1	606
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. rt, 40 h 3. rt, 6 h; then reflux, 5 h	 (10)	607
C_{12} 	$TiCl_4$, Zn	 R^1 R^2: Me H (70); H Me (60)	259
$C_{12–16}$ 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9 h 3. Reflux, 12 h	 n: 10 (76); 11 (52); 14 (85)	27
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9–30 h 3. Reflux, 12–14 h	n: 10 (76); 11 (52); 12 (71); 14 (85)	61 61 61, 27 61
C_{12} 	1. $TiCl_4$, Zn, py, THF, 0° 2. 0°, 4 h 3. rt, overnight	 (2.6) +  (16) +  (7)	227

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12} 	1. $TiCl_3$, Zn/Cu, DME, reflux, time 1 2. Reflux, time 2 3. Reflux, time 3	+  **I** **II**	
		Time 1 (h) / Time 2 (h) / Time 3 (h) / **I** / **II** 1 / 16 / 27 / (2) / (4)	608
		3 / 40 / 5 / (2.3) / (9)	609
C_{12-20} 	1. $TiCl_3$, Zn/Cu, DME, reflux, time 1 2. Reflux, 20 h 3. Reflux, time 2	 R / Time 1 (h) / Time 2 (h) H / 1.5 / 10 / (44)	238
		t-Bu / 12 / 12 / (45)	610
C_{12} 	1. $TiCl_3$, Zn, DME, reflux, 1 h 2. Reflux, 16 h 3. Reflux, 2 h	 (58)	207

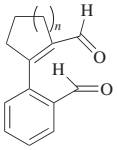
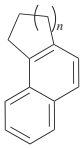
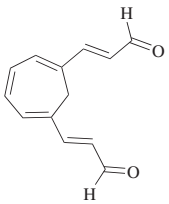
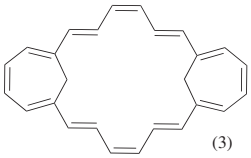
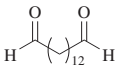
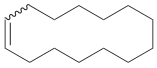
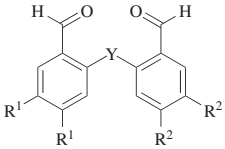
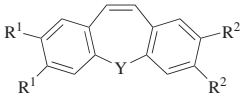
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-15} 	1. $TiCl_4$, Zn, THF, reflux, 2 h, 2. 0°, 30 min 3. Reflux, 2 h	 *n* 1 (65) 2 (65) 3 (65)	243
C_{13} 	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 15 h 3. Reflux, 4 h	+  (12) (3)	226
C_{14} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, 80°, 4 h 2. 80°, 35 h 3. 80°, 6 h	 (80) dr 9:1	6
	1. $TiCl_4$, Zn, py, THF, reflux, 2.5 h 2. rt, 4 h 3. rt, 16 h; then reflux, 4 h	 Y / R^1 / R^2 S / H / H / (95)	611
		S / MeO / H / (70)	612
		S / MeO / MeO / (80)	611
		Se / MeO / H / (73)	612
		Se / MeO / MeO / (80)	613
		Me_2Ge / H / H / (36)	613

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

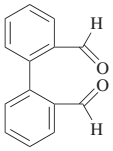
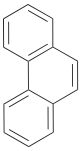
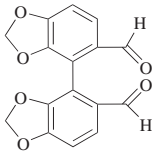
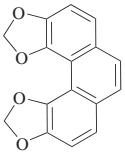
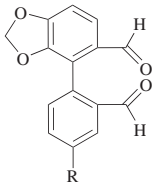
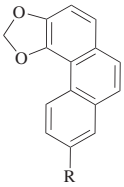
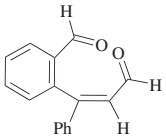
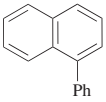
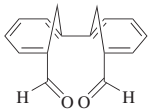
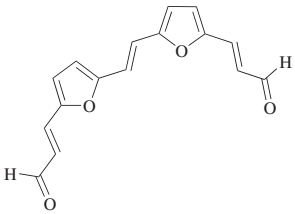
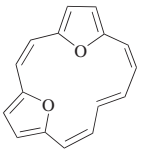
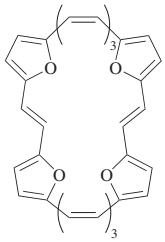
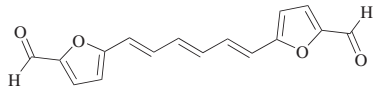
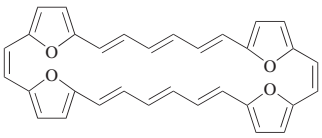
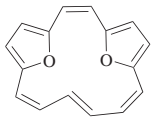
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h, 2. 0°, 30 min 3. Reflux, 2 h	 (67)	243
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. Reflux, 3 h 3. Reflux, 20 h	 (45)	614
	$TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 40 h	 R: H (57); MeO (45)	614
C_{16}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (60)	243
	$TiCl_4$, Zn, py, THF	(35–40)	225
	WCl_6, BuLi	(10)	225
	1. $TiCl_4$, Zn/Cu, py, reflux, 1 h 2. Reflux, 24 h 3. Reflux, 2 h	 (9) +  (6)	615
	1. $TiCl_4$, Zn/Cu, THF, reflux, 1 h 2. Reflux, 6.5 d 3. Reflux, 3 h	 (8) +  (7)	616

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

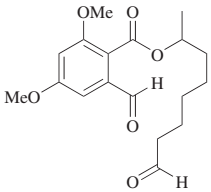
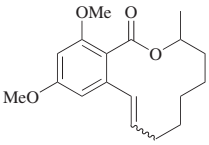
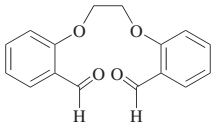
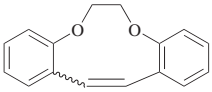
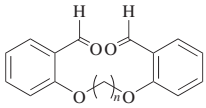
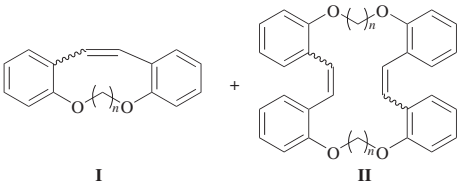
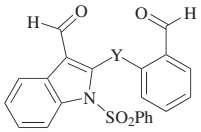
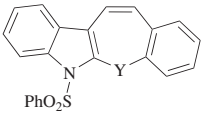
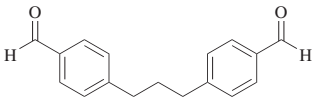
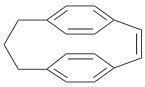
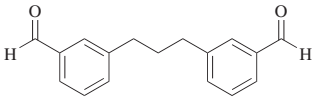
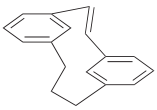
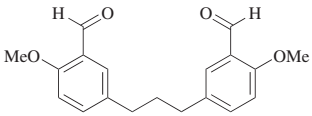
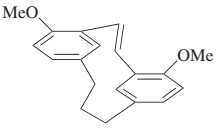
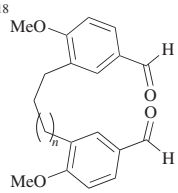
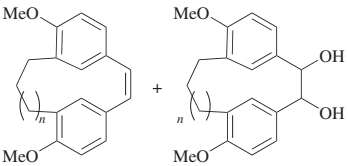
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}			
	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. rt, 10 h 3. Reflux, 5.5 h	 (60–82), (*E*)/(*Z*) = 3.5:1	617
	1. $TiCl_4$, Zn, solvent, reflux, 2.5 h 2. rt 3. Reflux, time	 Solvent / Time (h) / (*E*)/(*Z*) DME / 16 / (64) / 40:60 THF / 24 / (58) / 8:3	618 619
C_{16-18}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux	 **I** + **II** *n* / (*E*)-**I** / (*Z*)-**I** / **II** 2 / (57) / (23) / (12) 4 / (54) / (22) / (8)	620
C_{16}			
	1. $TiCl_4$, Zn, py, THF, reflux, 2.5 h 2. 4 h 3. rt, 16 h; then reflux, 4 h	 Y S (77) Se (73)	612
C_{17}			
	1. $TiCl_4$, Zn/Cu, py, DME, reflux, 2 h 2. Reflux, 60 h 3. Reflux, 12 h	 (14)	234
	1. $TiCl_4$, Zn/Cu, py, DME, reflux, 1 h 2. Reflux, 60 h 3. Reflux, 12 h	 (58)	234
	1. $TiCl_4$, Zn, THF 2. Py, reflux, 60 h 3. Reflux, 8 h	 (28)	621
C_{17-18}			
	1. $TiCl_4$, Zn, THF 2. Py, reflux, 60 h 3. Reflux, 8 h	 **I** + **II** *n* / **I** / **II** 1 / (23) / (65) 2 / (36) / (53)	622, 623 623

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

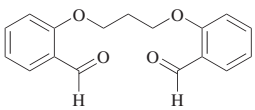
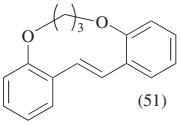
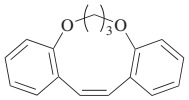
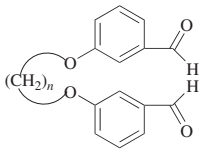
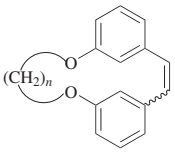
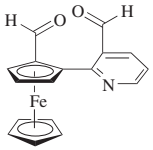
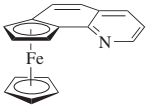
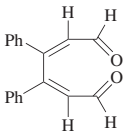
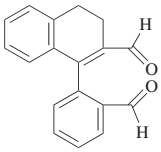
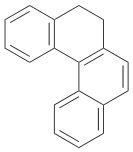
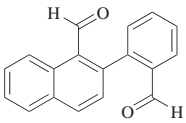
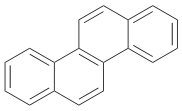
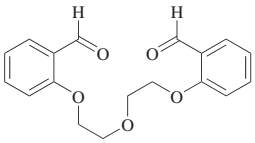
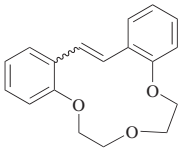
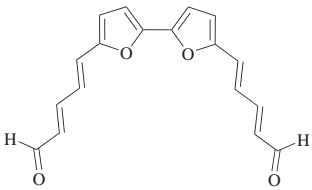
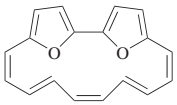
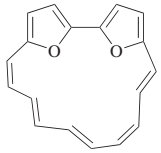
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17} 	$TiCl_4$, Zn, THF/toluene	 (51) +  (36)	624
C_{17-26} 	1. $TiCl_4$, Zn, THF, –10° 2. Dropwise addition, reflux 3. Reflux, 5 h	 *n* (65) (*E*)/(*Z*) 3 (65) 0:100 6 (95) 90:10 12 (64) 95:5	233
C_{17} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, rt 3. Reflux, 3 h	 (64)	625
C_{18} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	(60)	243
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (62)	243
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (58)	243
	1. $TiCl_4$, Zn, dioxane, reflux, 1 h 2. Dropwise addition, reflux 3. Reflux, 6.3 h	 (82.5), (*E*)/(*Z*) = 60:40	626
	1. $TiCl_4$, Zn, py, THF, reflux, 30 min 2. 100–110°, 18 h 3. 100–110°, 6 h	 (3) +  (9)	787a, 787b

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

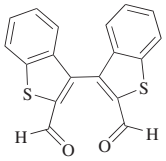
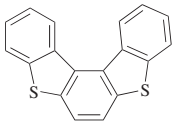
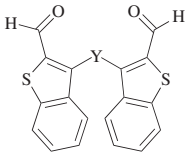
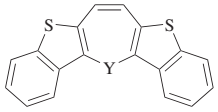
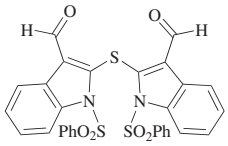
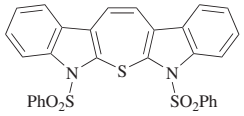
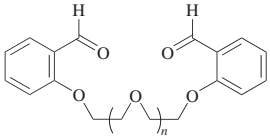
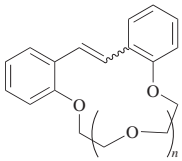
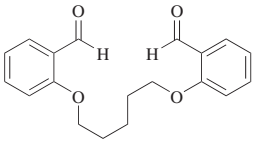
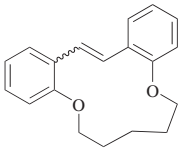
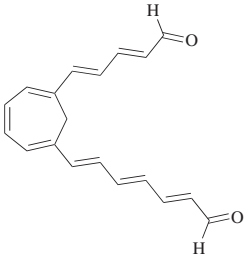
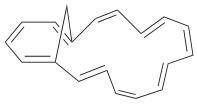
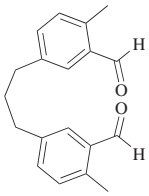
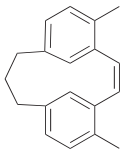
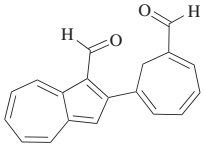
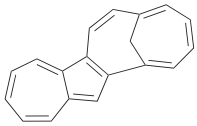
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}			
	1. $TiCl_4$, Zn, py, THF, reflux, 3 h 2. rt 3. Reflux, overnight	 (66)	627
	1. $TiCl_4$, Zn, py, THF, reflux, 2.5 h 2. rt, 4 h 3. rt, 16 h; then reflux, 4 h	 Y: S (86); Se (97); Me_2Si (75); Me_2Ge (81)	611 613 613 613
	1. $TiCl_4$, Zn, py, THF, reflux, 2.5 h 2. rt, 4 h 3. rt, 16 h; then reflux, 4 h	 (79)	611
C_{18-20}			
	$TiCl_4$, Zn, dioxane	 *n*: 1 (83) (*E*)/(*Z*) 60:40; 2 (43) 48:52	628
C_{19}			
	1. $TiCl_4$, Zn, dioxane, reflux, 1 h 2. Dropwise addition, reflux 3. Reflux, 20 h	 (63.5), (*E*)/(*Z*) = 38:62	626
	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 12 h 3. Reflux, 3 h	 (12)	226
	1. $TiCl_4$, Zn, THF 2. Reflux, 60 h 3. Reflux, 8 h	 (18)	629
	$TiCl_3$, $LiAlH_4$	 (5–10)	630

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

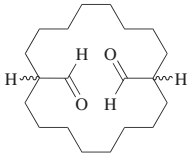
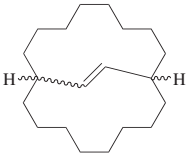
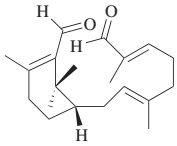
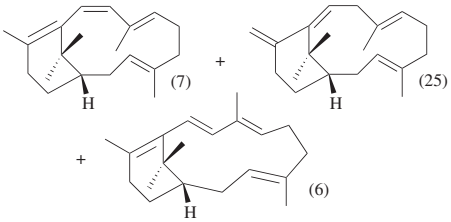
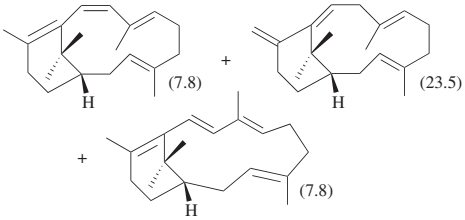
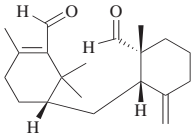
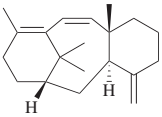
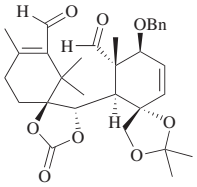
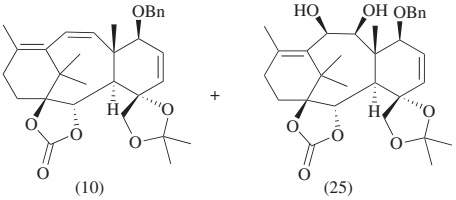
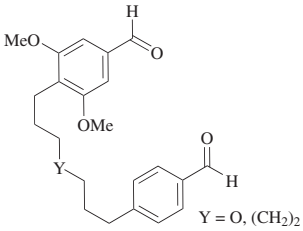
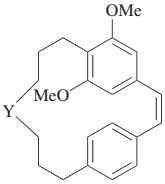
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME 2. Reflux, 24 h 3. Reflux, 3.5 h	 (19.5)	631
	1.$TiCl_3$, Zn/Cu, DME 2. 22 h	 (7) + (25) + (6)	272
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 22 h 3. Reflux, 3 h	 (7.8) + (23.5) + (7.8)	271
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 24 h 3. Reflux, 18 h	 (20)	262
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3.5 h 2. 70°, 1 h 3. 70°, 30 min	 (10) + (25)	261
C_{20-22}			
 Y = O, $(CH_2)_2$	1. $TiCl_4(THF)_2$, Zn, THF, reflux, 30 min 2. Reflux 3. Reflux, 3 h	 (5–15)	632

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

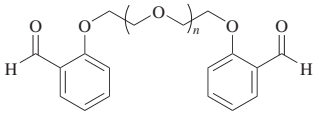
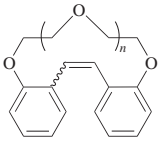
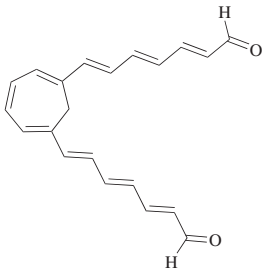
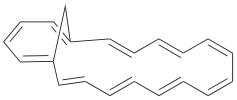
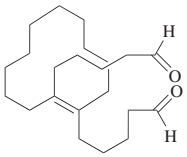
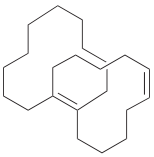
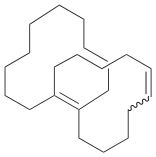
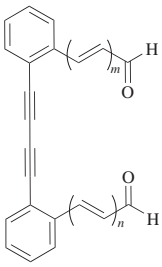
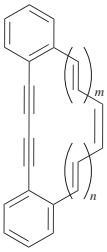
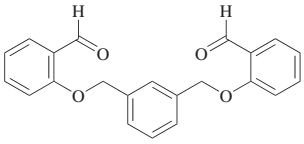
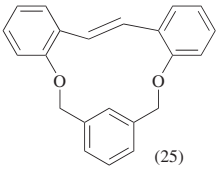
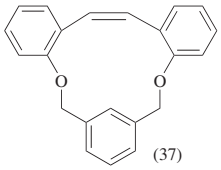
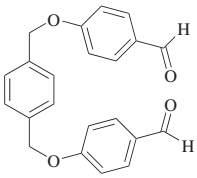
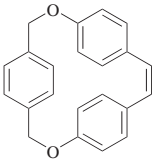
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20-26} 	1. $TiCl_4$, Zn/Cu, THF, reflux, 30 min 2. Reflux, 50 h 3. Reflux, 1 h	 *n* (*E*)/(*Z*) 2 (95) 48:52 3 (93) 65:35 4 (91) 35:65 5 (94) 60:40	633
C_{21} 	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 14 h 3. Reflux, 4 h	 (4.5)	226
C_{22} 	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 34 h 3. Reflux, 14 h	 (40)	634
	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 16 h 3. Reflux, 3 h	 (44)	219
C_{22-30} 	1. $TiCl_3$, $LiAlH_4$, solvent, reflux, time 1 2. Reflux, time 2 3. Reflux, 5 h	 *m* *n* Solvent Time 1 (min) Time 2 (h) 1 1 THF 15 10 (27) 1 2 DME 30 8 (20) 2 2 DME 30 6 (14) 2 3 DME 30 8 (8.7) 3 3 DME 30 10 (4)	229
C_{22} 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Dropwise addition, reflux 3. Reflux, 6 h	 (25) +  (37)	635
	$TiCl_4$, Zn, THF, 24 h	 (53)	636

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

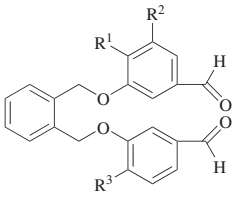
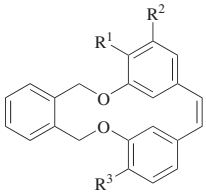
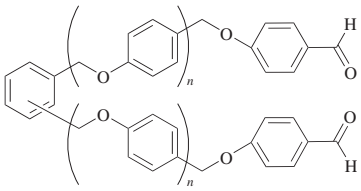
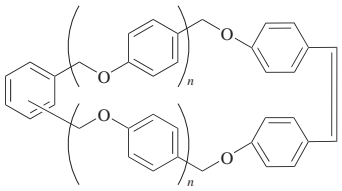
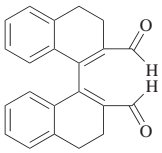
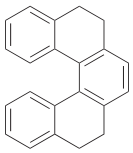
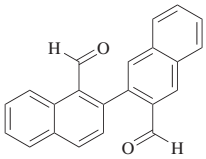
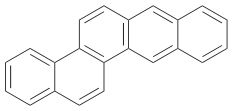
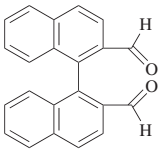
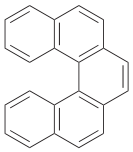
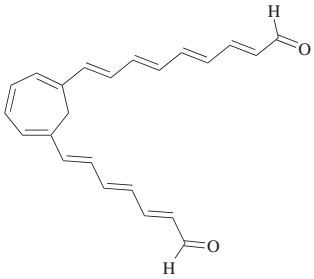
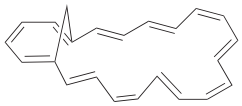
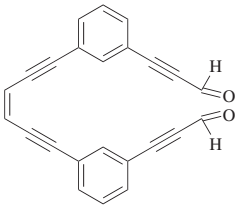
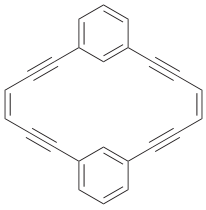
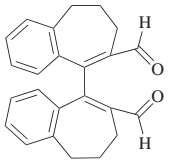
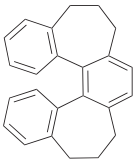
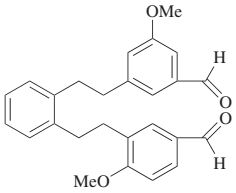
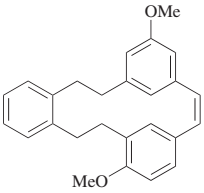
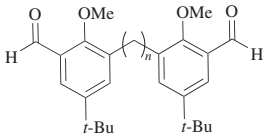
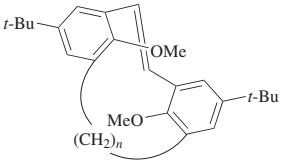
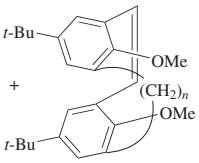
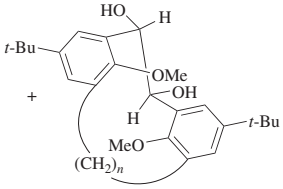
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{22} 	1. $TiCl_3$, Zn/Cu, THF, reflux, 1 h 2. Reflux, 8 h 3. Reflux, 13 h	 R^1 R^2 R^3 H H H (62) MeO H H (57) H MeO MeO (65) MeO H MeO (65) H H MeO (10)	637
$C_{22–36}$ 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 16 h 3. Reflux, 24 h	 *n* Isomer 0 2- (55) 0 3- (60) 0 4- (53) 1 2- (25) 1 3- (30) 1 4- (35)	638
C_{22} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (62)	243
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (57)	243
	$TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux	 (21)	639
C_{23} 	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 12 h 3. Reflux, 3 h	 (7.5)	226
C_{24} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. –78°, 5 h	 (69)	640

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. 0°, 30 min 3. Reflux, 2 h	 (58)	243
	$TiCl_3$, Zn/Cu, THF, reflux	 (65)	641
C_{24-27} 	1. $TiCl_4$, Zn, THF 2. Reflux, 60 h 3. Reflux, 8 h	 **I** +  **II** +  **III** | *n*	**I**	**II**	**III**
2	(0)	(0)	(18.3)
3	(0)	(1.0)	(29.1)
4	(2.1)	(2.0)	(56.5)
5	(0)	(27.4)	(15.3)		642

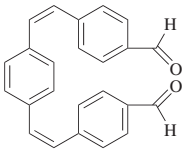
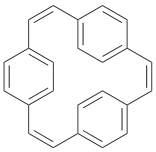
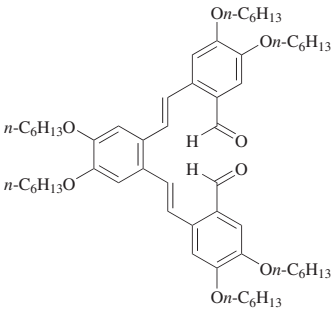
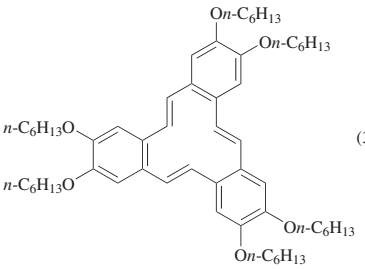
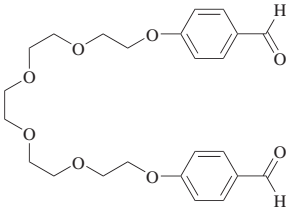
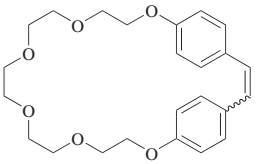
C_{24} 	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. "Several h" 3. Reflux	 (50)	643
	$TiCl_3$, Zn/Cu	 (37)	644
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 30 min 3. Reflux, 30 min	 (61), (*E*)/(*Z*) = 46:54	85

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

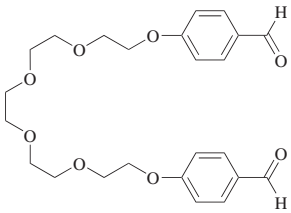
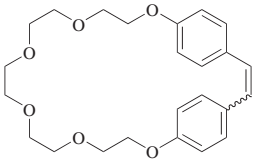
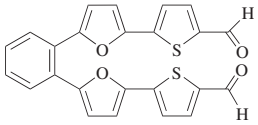
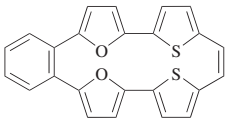
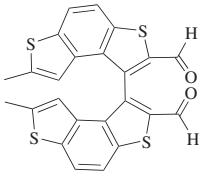
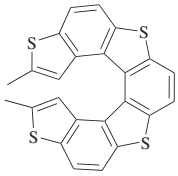
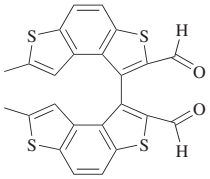
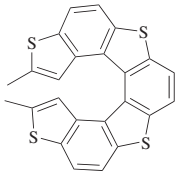
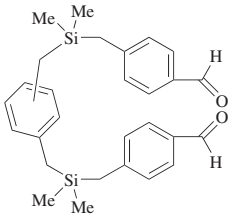
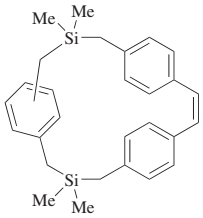
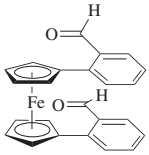
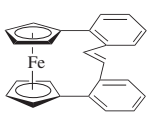
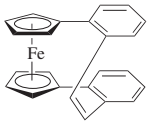
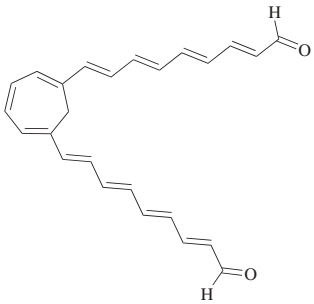
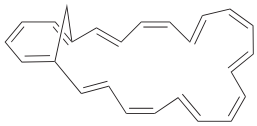
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}			
	1. Ti, TMSCl, DME, reflux, 24 h 2. Reflux, 45 min 3. Reflux, 6 h	 (52) dr 72:28	85
	$TiCl_4$, Zn, py, THF, reflux, 5 h	 (18)	151
	$TiCl_3(DME)_{1.5}$, Zn/Cu, DME	 (78)	645
 **I**	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 2 h 3. Reflux, 36 h	 **II** (*P*)–**II**; (52) er >99.5:0.5 from (*S*)–**I** (*M*)–**II**; (53) er >99.5:0.5 from (*R*)–**I**	245
	1. $TiCl_4$, Zn, DME, reflux, 1 h 2. Dropwise addition, rt 3. Reflux, 24 h	 Isomer 2- (13) 3- (10)	356
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, 21 h 3. Reflux, 10 h	 (5.3) +  (14.3)	646
C_{25}			
	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 12 h 3. Reflux, 4 h	 (7.3)	226

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

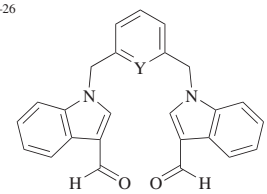
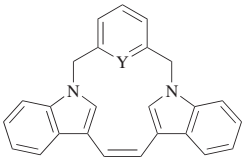
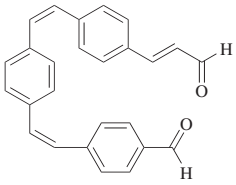
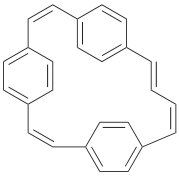
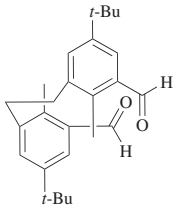
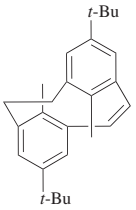
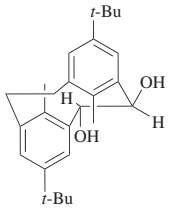
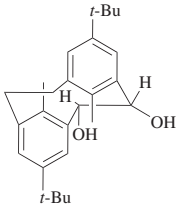
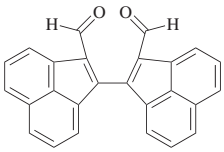
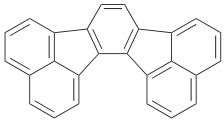
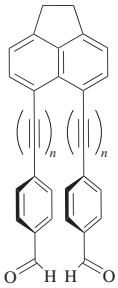
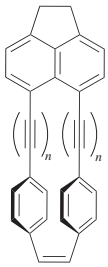
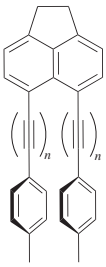
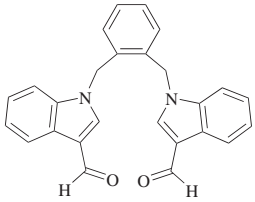
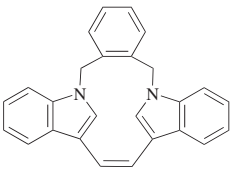
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{25-26} 	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, overnight	 Y: N (36); CH_2 (24)	647 648, 647
C_{26} 	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. Dropwise addition, reflux 3. Reflux	 (48)	649
	$TiCl_4$, Zn, py, THF, reflux, 60 h	 (4.3) +  (7.3) +  (1.5)	650
	1. $TiCl_4$, Zn, THF, reflux, 2 h, 2. 0°, 30 min 3. Reflux, 2 h	 (56)	243
C_{26-30} 	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Py, reflux, 9.5 h 3. Reflux, 10 h	 +  + **I** **II** **III** n / **I** / **II** / **III**: 0 (24) (12.5) (2.5); 1 (32) (8.5) (15)	651
C_{26} 	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, overnight	 (19)	648, 647

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

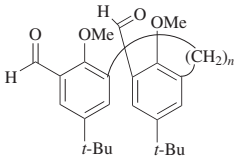
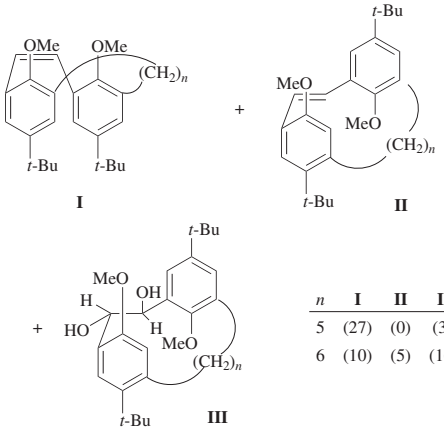
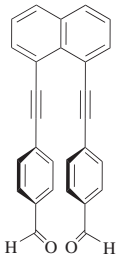
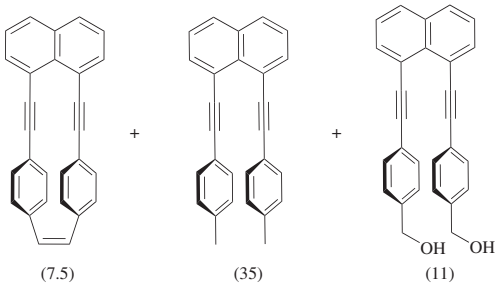
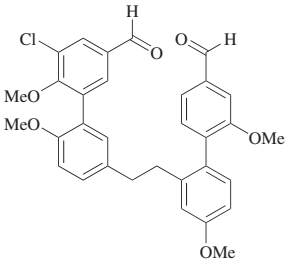
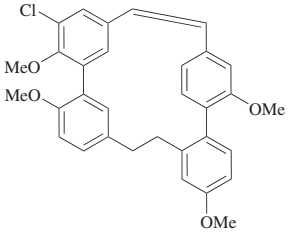
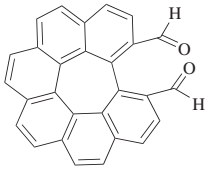
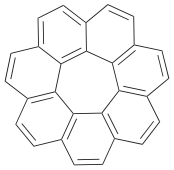
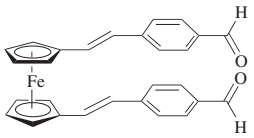
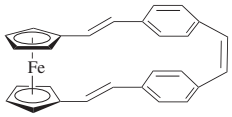
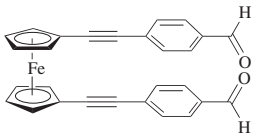
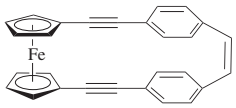
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{27–28}$			
	1. $TiCl_4$, Zn, THF 2. Reflux, 60 h 3. Reflux, 8 h	 **I** + **II** + **III** n **I** **II** **III** 5 (27) (0) (32) 6 (10) (5) (16)[b]	652
C_{28}			
	1. $TiCl_4$, $LiAlH_4$, THF, reflux, 2 h 2. Bu_3N, reflux, 8 h 3. Reflux, 10 h	 (7.5) + (35) + (11)	651
	1. $TiCl_3(DME)_2$, Zn/Cu, DME, 80°, 5 h 2. 80°, 6 h 3. 80°, 8 h	 (70)	653
	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Dropwise addition, reflux 3. Reflux, 4 h	 (35)	244, 654
	1. $TiCl_4$, $LiAlH_4$, THF, 0°, 20 min 2. Reflux, 6 h 3. Reflux, 7 h	 (2.2)	655, 656
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Py, reflux, 11 h 3. Reflux, 10 h	 (15)	655, 656

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

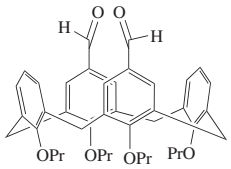
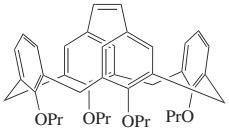
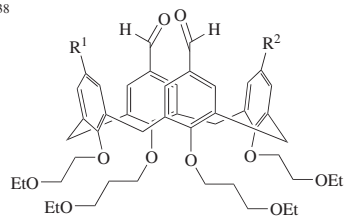
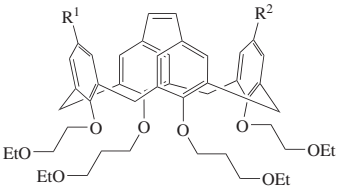
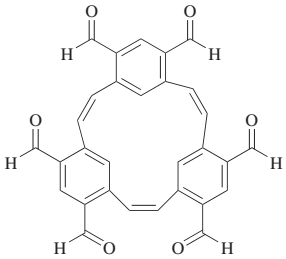
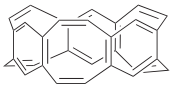
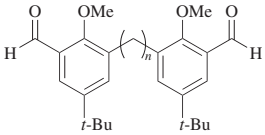
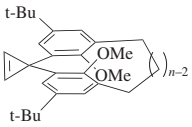
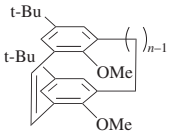
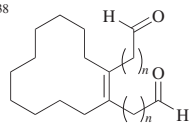
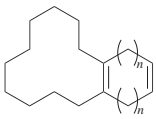
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{30} 	1. $TiCl_3$, Zn, THF 2. Reflux, 2 h 3. Reflux, 15 h	 (30)	241
C_{30-38} 	1. $TiCl_4$, Mg, $HgCl_2$, THF, –10° 2. –10° 3. –10°, 20 min; then rt, time	 R^1 R^2 Time H H 16 h (30) Me H 10 h (27) Me Me 10 h (15) *t*-Bu *t*-Bu 40 min (25)	240
C_{30} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, 100°, 2 h 2. Dropwise addition, 95° 3. 95°, 5 h; then rt, overnight	 (8)	657, 232
C_{30-32} 	1. $TiCl_4$, Zn, THF 2. Reflux, 60 h 3. Reflux, 8 h	 **I** +  **II** *n* **I** **II** 8 (13) (48) 10 (52) (42)	658
C_{32-38} 	$TiCl_3$, Li, DME, heat, 20 h	 *n* 9 (77) 10 (70) 12 (75)	659

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

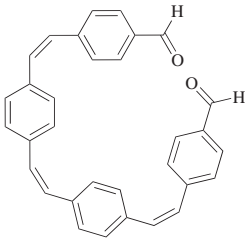
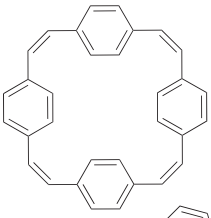
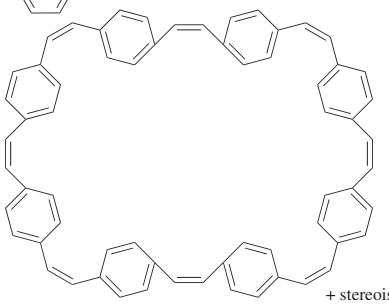
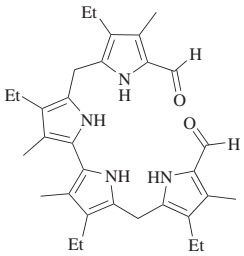
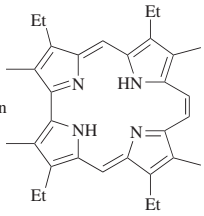
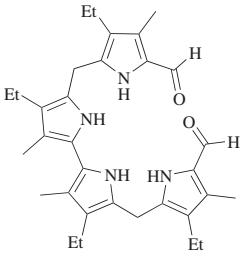
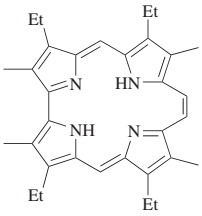
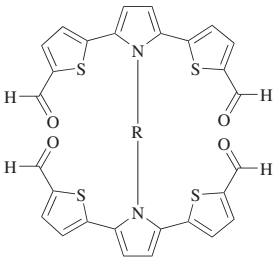
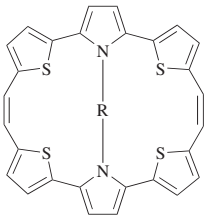
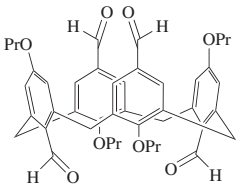
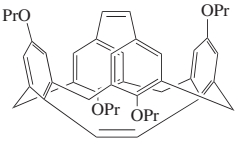
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{32} 	1. $TiCl_4$, Zn, THF/toluene, reflux, 2 h 2. rt, 30 min 3. rt, 12 h; then reflux, 5 h	 (21) + stereoisomers +  (37) + stereoisomers	314
	$TiCl_4$, Zn, THF, then air oxidation	 (2)	660
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 1 h 2. 0°, 30 min 3. 0°, 5 min 4. $FeCl_3$, 2 h	 (3)	661
C_{32-38} 	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1.5 h 2. Reflux 3. Reflux, 18 h	 R: $(CH_2)_4$ (58); $(CH_2)_6$ (24); $[(CH_2)_3O(CH_2)_2]_2O$ (51)	662
C_{32} 	1. $TiCl_3$, Zn, THF 2. Reflux, 2 h 3. Reflux, 15 h	 (25)	241

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

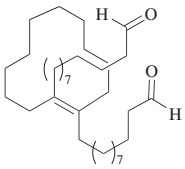
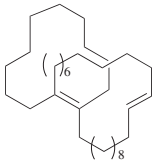
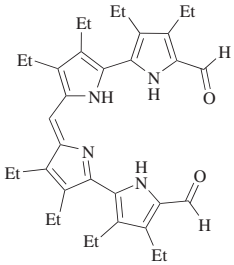
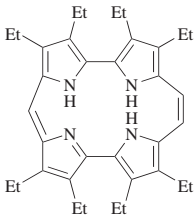
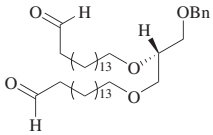
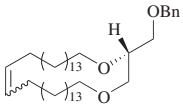
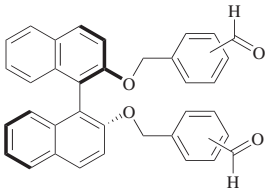
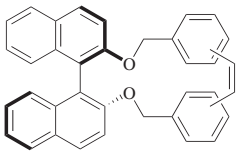
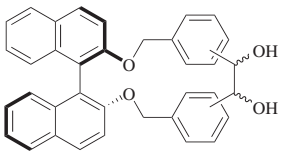
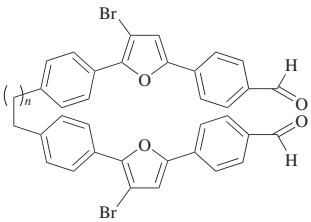
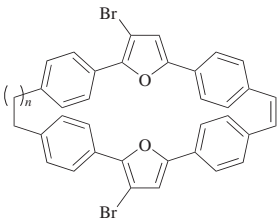
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{34} 	1. $TiCl_3$, Li, DME, reflux, 2 h 2. Reflux, 16 h 3. Reflux, 3 h	 (56)	219
C_{35} 	1. $TiCl_4$, Zn, CuCl, THF, reflux, 2 h 2. Reflux, 20 min 3. Reflux, 5 min 4. $FeCl_3$	 (23)	663
	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 100 h 3. Reflux 14 h	 (53) dr 4:1	664
C_{36} 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, 12 h	 **I** +  **II** Isomer **I** **II** 2- (52) (8) 3- (62) (7) 4- (15) (50)	237
$C_{36–46}$ 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux 3. Reflux, 16 h	 *n* 1 (66) 2 (38) 3 (25) 4 (32) 5 (25) 11 (75)	665

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

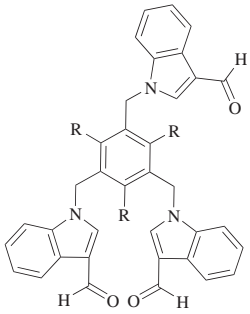
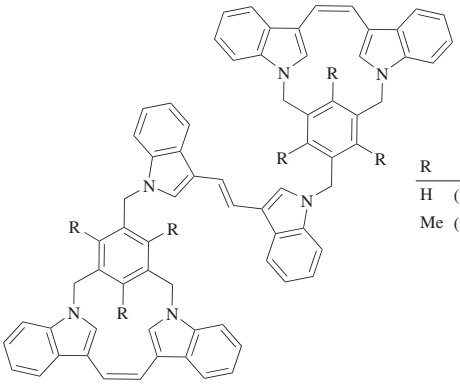
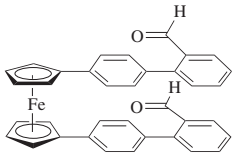
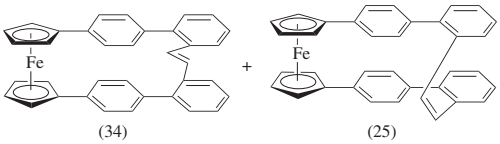
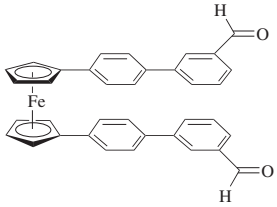
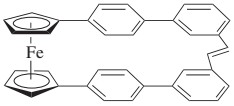
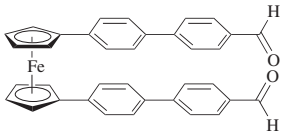
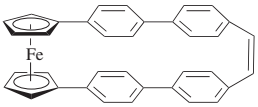
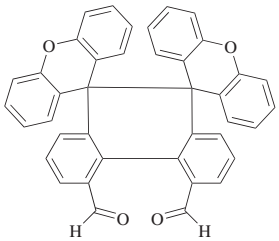
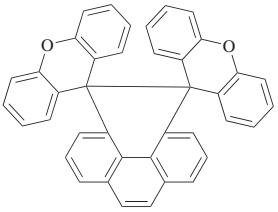
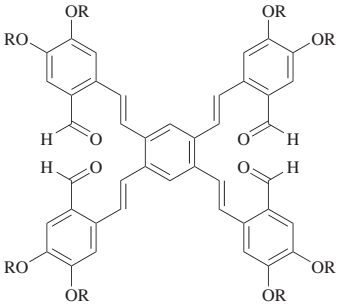
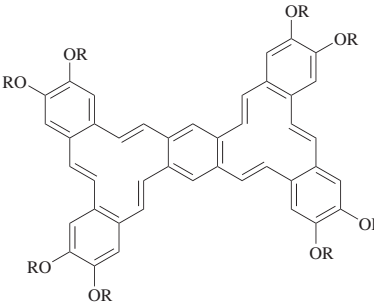
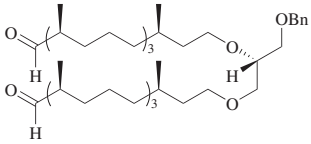
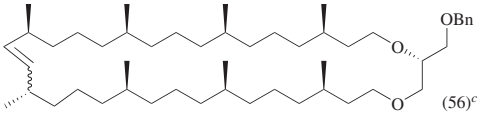
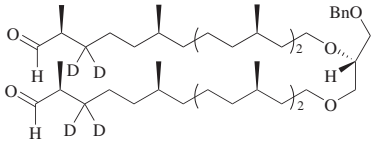
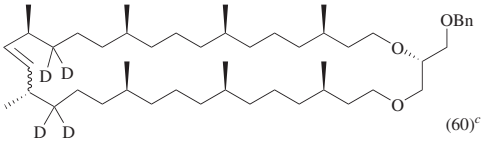
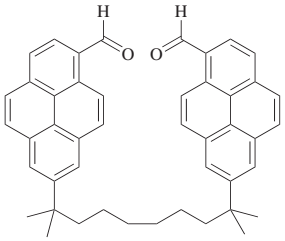
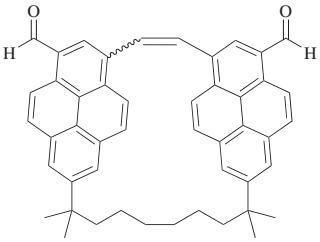
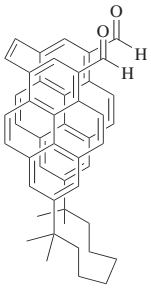
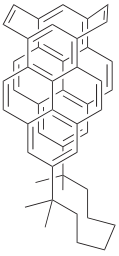
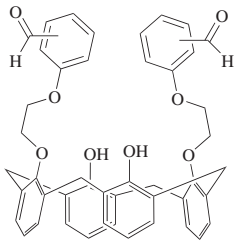
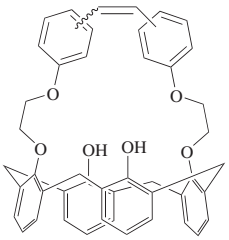
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{36–39}$			
	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, overnight	 R H (24) Me (22)	666, 647
C_{36}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, 18 h 3. Reflux, 10 h	 (34) + (25)	239
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, 18 h 3. Reflux, 10 h	 (28)	239
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Py, reflux, 18 h 3. Reflux, 10 h	 (32)	239
C_{40}			
	$TiCl_4$, Zn, THF	 (22)	667
C_{42}			
 R = *n*-C_6H_{13}	$TiCl_3$, Zn/Cu	 (13)	644

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{43}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1.5 h 2. Reflux, 50 h 3. Reflux, 18 h	 (56)[c]	668, 669
	1. $TiCl_3$, Zn/Cu, DME, reflux, 2 h 2 Reflux, 44 h 3. Reflux, 18 h	 (60)[c]	670
C_{46}			
	$TiCl_4$, Zn, py, 0° to reflux, 5 h; then Rieche formylation	 (*E*) (11), (*Z*) (57)	671
	$TiCl_4$, Zn, py, 0° to reflux, 4 h	 (41)	671
	$TiCl_4$, Zn, THF		242

Isomer	(*E*)	(*Z*)
2-	(15)	(62)
3-	(37)	(37)
4-	(—)	(87)

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

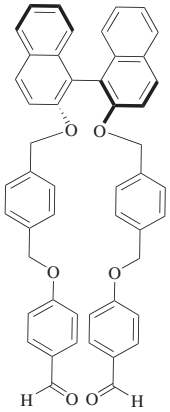
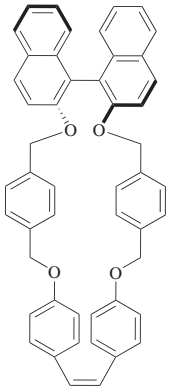
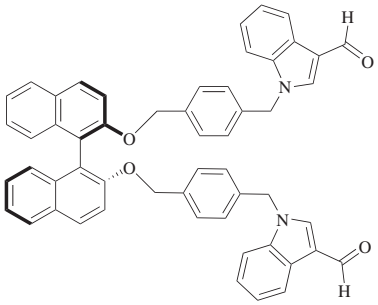
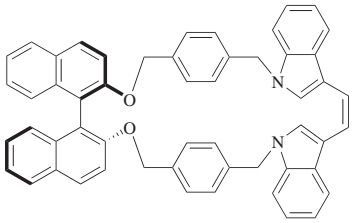
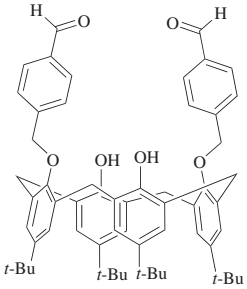
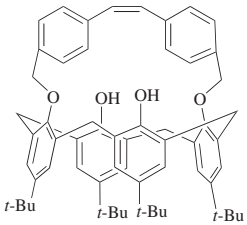
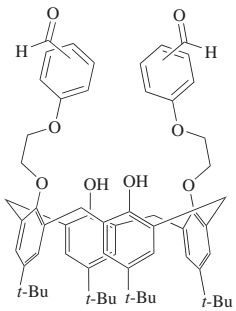
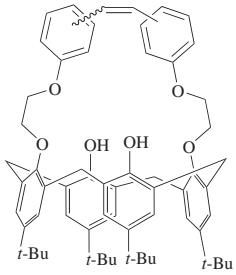
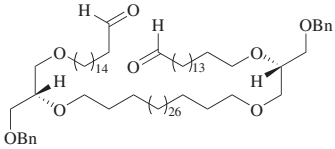
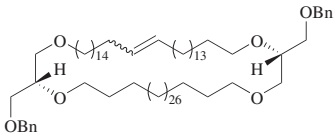
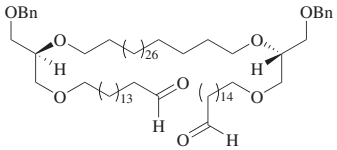
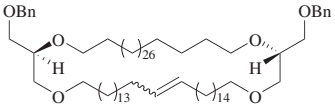
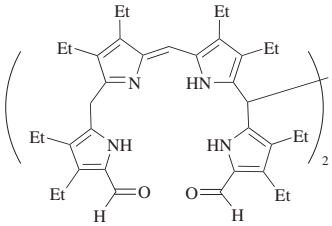
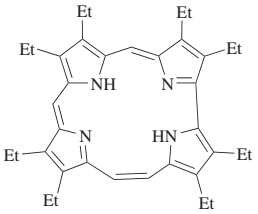
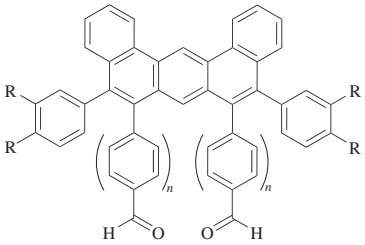
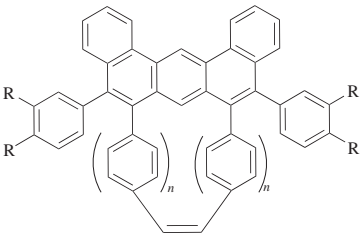
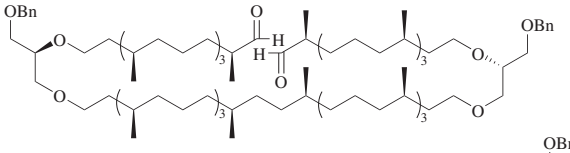
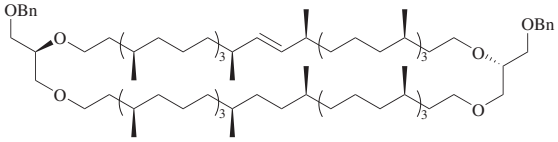
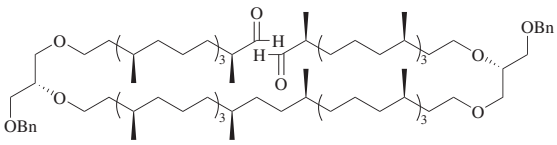
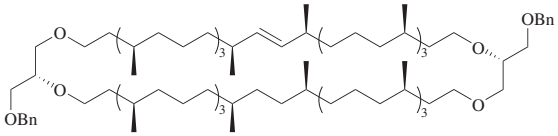
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{50} 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, 12 h	 (40)	237
C_{54} 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, 12 h	 (15)	237
C_{60} 	$TiCl_4(THF)_2$, Zn, THF, reflux, 20 h	 (42)	672
C_{62} 	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Dropwise addition, reflux 3. Reflux, 15 h	 Isomer (*E*) (*Z*) 2- (10) (57) 3- (8) (20) 4- (0) (51)	673, 674
C_{70} 	1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 50 h 3. Reflux, 11 h	 (66), (*E*)/(*Z*) ~4:1	675, 147

TABLE 3A. INTRAMOLECULAR COUPLING OF DIALDEHYDES (*Continued*)

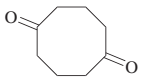
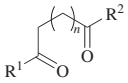
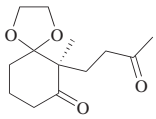
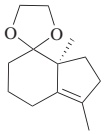
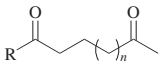
Dialdehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{70}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 50 h 3. Reflux, 11 h	 (61), (*E*)/(*Z*) ~4:1	675, 147
C_{72}			
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 1 h 2. rt, 10 min; then oxidation with I_2	 (20)	676
 R = O*n*-C_6H_{13}	1. $TiCl_4$, Zn, THF, 80°, 1 h 2. Py, 80°, 10 h 3. Reflux, overnight	 *n*: 1 (63); 2 (67)	315
C_{86}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 45 h 3. Reflux, 18 h	 (59)	677
	1. $TiCl_3$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 45 h 3. Reflux, 18 h	 (66)	677

[a] The product was isolated as *trans*-1,2-dibromocyclohexane.

[b] This product was isolated as the diacetate.

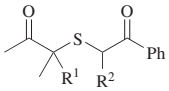
[c] The product was a single isomer. The stereochemistry was not rigorously determined.

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES

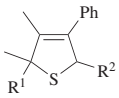
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 18 h 3. Reflux, 24 h	(32)	678
C_{11-19} 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 30 h 3. Reflux, 14 h		61
C_{11} 	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 30 h	 (75)	84, 679
C_{12-15} 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9 h 3. Reflux, 12 h		27

n	R^1	R^2	
1	Ph	Ph	(87)
2	Me	Ph	(70)
3	Me	Bu	(79)
3	Ph	Ph	(95)
3	Me	$Ph(CH_2)_2$	(50)
5	Bu	Bu	(67)
6	Bu	Bu	(68)
7	Bu	Bu	(75)
8	Bu	Bu	(76)

n	R	
1	Ph	(70)
2	n-C_7H_{15}	(79)
2	$Ph(CH_2)_2$	(50)

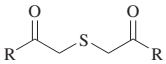
C_{12-18} 

$TiCl_4$, Zn, THF, reflux, 5 h



R^1	R^2	
H	H	(82)
Me	H	(81)
H	Me	(63)
H	Ph	(76)

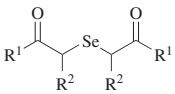
680



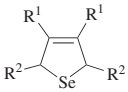
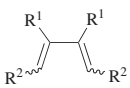
$TiCl_4$, Zn, dioxane, rt, 4 h; then 50°, 2 h

R	
Ph	(62)
2-C_4H_3S	(66)
4-MeC_6H_4	(68)
4-$MeOC_6H_4$	(70)
4-BrC_6H_4	(68)

680



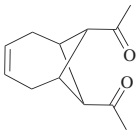
1. $TiCl_4$, Zn, THF
2. Dropwise addition, reflux
3. Reflux, time

 + 

I **II**

R^1	R^2	Time (h)	**I**	**II**
2-C_4H_3S	H	2	(24)	(28)
Ph	H	2	(16)	(31)
Ph	Me	4	(20)	(35)
4-ClC_6H_4	H	2	(30)	(36)
4-MeC_6H_4	H	2	(13)	(26)

681

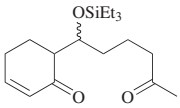
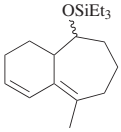
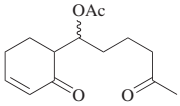
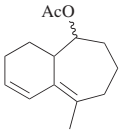
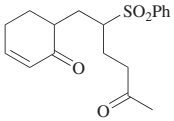
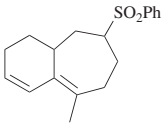
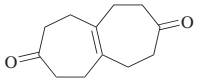
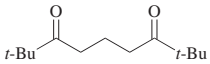
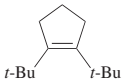
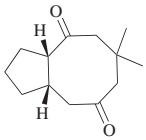
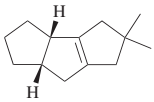
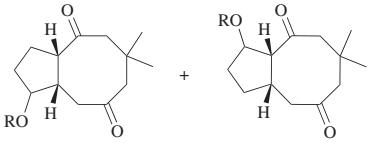
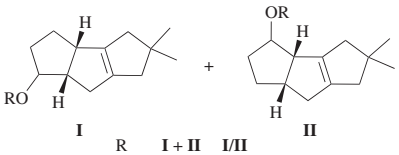
C_{12} 

1. $TiCl_3(THF)_3$, K, DME, reflux, 1h
2. rt
3. Reflux, 15 h

(13)

682, 222

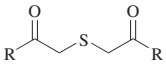
TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}			
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 3 h	 (74)	679, 84
	1. $TiCl_4$, Na-$C_{10}H_8$, THF, reflux, 30 min 2. rt, 10 h 3. Reflux, 4 h	 (58)	679, 84
	1. $TiCl_4$, Na-$C_{10}H_8$, THF, reflux, 30 min 2. rt, 10 h 3. Reflux, 4 h	 (39) single isomer	84
	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 48 h	(50)[a]	223
C_{13}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 1.5 h 2. Reflux 3. Reflux, 92 h	 (85)	320
	$TiCl_3$, K, THF, reflux, 6 d	 (—)	683
	1. $TiCl_3$, K, THF, reflux, 1 h 2. rt 3. Reflux, 4 d		248

I **II**

R	I + II	I/II
H	(—)	100:0
TBS	(59)	38:21

$C_{14–24}$

	$TiCl_4$, Zn		684, 685

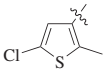
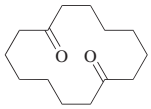
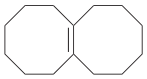
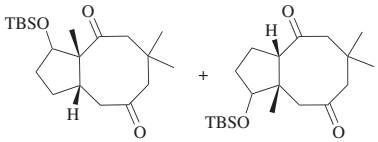
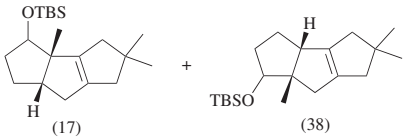
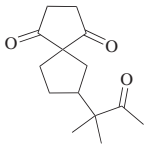
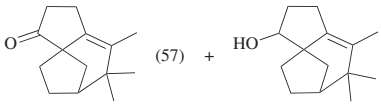
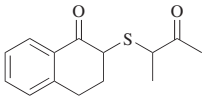
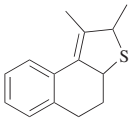
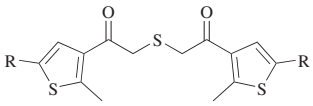
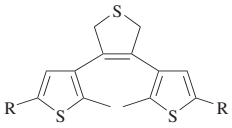
R	
Ph	(—)
4-ClC_6H_4	(—)
4-BrC_6H_4	(—)
4-Tol	(—)
2-Np	(—)
	(—)
	(—)

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 24 h 3. Reflux, 6 h	 (72)	221
 1:2	$TiCl_3$, K, THF, reflux	 (17) + (38)	686
	1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 50.5 h 3. Reflux, 84 h	 (57) + (21)	255, 256
	$TiCl_4$, Zn, THF, reflux, 5 h	 (44)	680
$C_{14–16}$			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Additive, temp 1, time 1 3. Temp 2, time 2		

R	Additive	Temp 1	Time 1 (h)	Temp 2	Time 2 (h)		Refs.
Cl	—	rt	24	rt	24	(70)	687
Me	py	20°	—	reflux	6	(11)	688

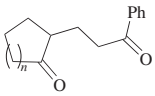
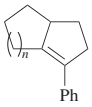
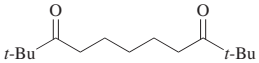
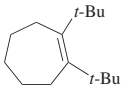
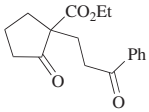
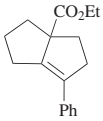
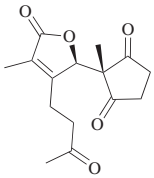
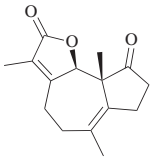
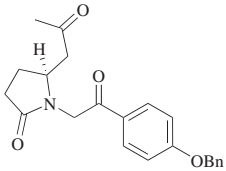
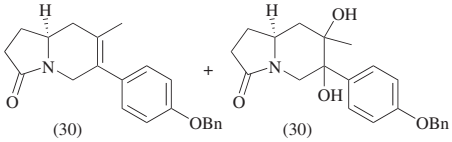
$C_{14–15}$			
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 3 h	 *n*: 1 (86); 2 (87)	84, 679
C_{15}			
	$TiCl_4$, $LiAlH_4$, THF, reflux, 15 h	 (10)	148
	1. $TiCl_4$, Na/Hg, DME, reflux, 5 h 2. rt, 10 h 3. Reflux, 4 h	 (73)	84, 679
	1. $TiCl_4$, Zn, THF, rt, 30 min 2. 0° 3. Reflux, 4 h	 (45)	689
	1. $TiCl_3(THF)_3$, Zn/Cu, DME, 80°, 4 h 2. 80°, 5 h 3. 80°, 40 h	 (30) + (30)	252, 690

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

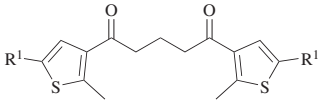
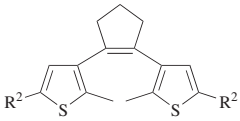
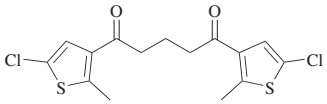
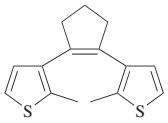
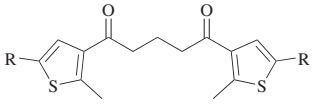
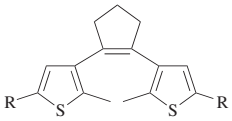
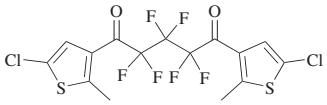
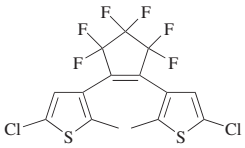
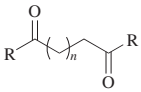
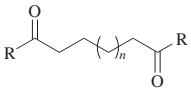
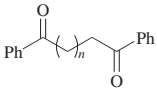
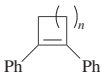
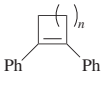
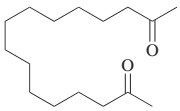
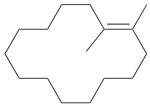
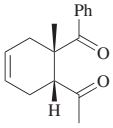
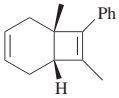
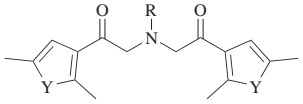
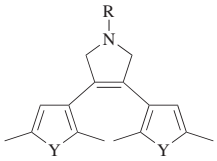
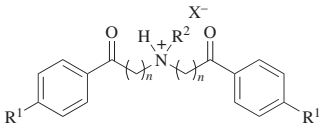
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-17} 	1. $TiCl_3(THF)_3$, Mg, THF, 40° 2. 40° 3. 40°, time	 R^1 R^2 Time (h) Cl H 0.5 (20) Me Me 2 (58)	691
C_{15} 	1. $TiCl_4$, Zn, THF, reflux, 45 min 2. 0° 3. Reflux, 2 h	 (50)	691
C_{15-17} 	$TiCl_3(THF)_3$, M, THF, 40°	 R M H Mg (—) Cl Zn (44) Me Zn (—)	692
C_{15} 	$TiCl_3(THF)_3$, Zn, THF, 40°, 1 h	 (55)	693, 691
C_{16-24} 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9 h 3. Reflux, 12 h	 *n* R 1 Ph (87) 5 *n*-C_5H_{11} (67) 6 *n*-C_5H_{11} (68) 7 Bu (75) 8 Bu (76) 9 Pr (71) 10 Pr (65) 11 Et (75) 13 Me (90) 19 Me (83)	27
	1. $TiCl_3$,Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 2 h 3. Reflux, time	 *n* R Time (h) 1 Ph 1.5 (76) 7 Ph 3 (72) 9 Me 1 (39)	69
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 15 min 2. Reflux, 0.5–1 h 3. Reflux, time	 *n* Time (d) 1 1 (40–61) 2 6 (62) 3 1 (35) 3 5 (60) 5 6 (61) 6 6 (53) 7 6 (49) 9 6 (61)	146, 694 146 146, 694 146 146 146 146 146
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 6–8 h 3. Reflux, 14 h	 *n* 1 (70) 3 (87) 9 (89)	73, 74

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

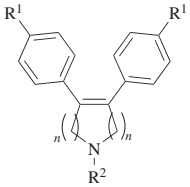
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16} 	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. Reflux, 35 h 3. Reflux, 8 h	 (82)	6
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 19 h 3. Reflux, 12 h	 (97)	695
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Reflux, 8 h 3. Reflux, 24 h		696

Y	R	
S	Ph	(—)
S	4-$MeOC_6H_4$	(—)
S	4-ClC_6H_4	(—)
S	4-MeC_6H_4	(—)
S	Bn	(—)
O	Ph	(—)
O	4-$MeOC_6H_4$	(—)
O	4-ClC_6H_4	(—)

C_{16-20}



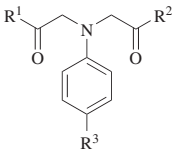
1. $TiCl_4$, Zn, THF, reflux, 1 h
2. rt
3. Reflux, 6 d



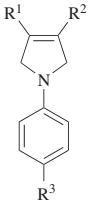
n	X	R^1	R^2	
1	Br	H	Bn	(90)
1	Br	H	4-MeC_6H_4	(91)
2	Cl	H	Me	(63)
2	Cl	H	Et	(60)
2	Cl	H	Bu	(66)
2	Cl	Me	Me	(56)

426

C_{16}



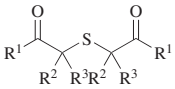
1. $TiCl_4$, Zn, THF, reflux, 1 h
2. rt
3. rt, 24 h



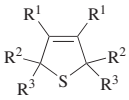
R^1	R^2	R^3	
Ph	Ph	H	(74)
Ph	Ph	MeO	(85)
Ph	Ph	Cl	(66)
Ph		MeO	(61)
		MeO	(80)

697

C_{16-24}



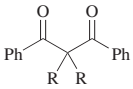
$TiCl_4$, Zn



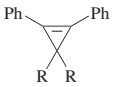
R^1	R^2	R^3	Solvent	Temp	Time (h)	
Ph	H	H	dioxane	rt	18	(67)
Ph	H	H	THF	reflux	5	(77)
Ph	Me	H	THF	reflux	5	(73)
Ph	Et	H	THF	reflux	5	(86)
Ph	Me	Me	THF	reflux	5	(75)
2-Np	H	H	THF	reflux	5	(71)

680

C_{17-19}



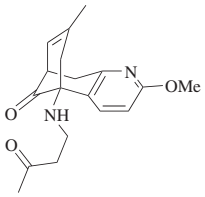
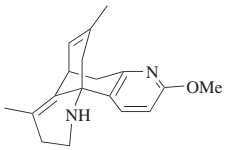
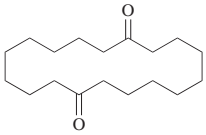
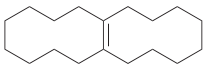
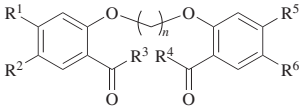
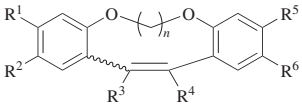
1. $TiCl_3$, $LiAlH_4$, THF, reflux, 15 min
2. Reflux, 0.5–1 h
3. Reflux, 6 d



R	
Me	(46)
Et	(40)

146

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17} 	$TiCl_4$, Zn, py, THF, reflux, 20 h	 (62)	253
C_{18} 	$TiCl_3$, Li	 (34–70)	698
C_{18-20} 	1. $TiCl_4$, Zn, solvent, reflux, 2.5 h 2. rt 3. Reflux, time		

n	R^1	R^2	R^3	R^4	R^5	R^6	Solvent	Time (h)	(E)/(Z)		Refs.
2	H	H	Me	Me	H	H	DME	16	2:98	(80)	618
2	H	H	Me	Me	EtO	H	DME	16	10:90	(56)	618
2	H	H	Me	Et	H	H	DME	16	5:95	(56)	618
2	H	H	Me	Me	H	Me	DME	16	4:94	(76)	618
2	H	H	Me	Me	H	H	THF	1	1:3	(70)	619
2	H	MeO	Me	Me	H	MeO	THF	1.5	1:3	(65)	619
2	H	H	Et	Et	H	H	THF	1.5	3:8	(75)	619
2	Me	H	Me	Me	H	H	THF	1.5	3:7	(63)	619
4	H	H	Me	Me	H	H	DME	16	8:92	(75)	618
4	H	H	Me	Me	H	H	THF	6	1:3	(52)	619

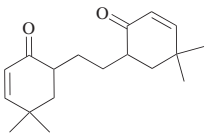
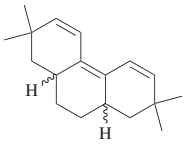
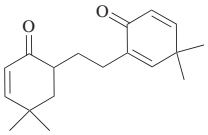
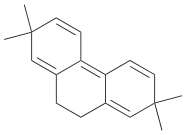
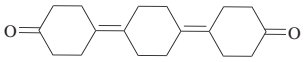
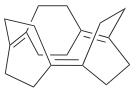
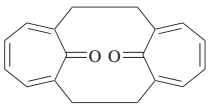
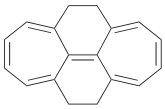
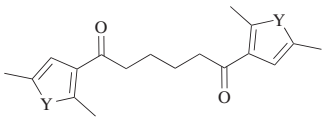
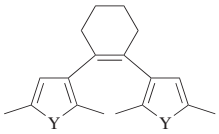
C_{18} 	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 10 h 3. Reflux, 12 h	 (51) dr 1:1.7	200
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux, 10 h 3. Reflux, 12 h	 (55)	200
	1. $TiCl_3$, Zn/Cu, DME, reflux, 5 h 2. 68°, 45 h 3. 68°, 2 h	 (24)	699, 230
	$TiCl_4$, Zn, THF	 (90–95)	700
	1. $TiCl_4$, Zn, THF or dioxane, reflux, 1 h 2. 20° 3. Reflux, 20 h	 Y: O (33), S (25)	688

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

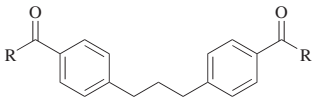
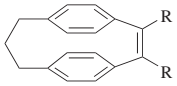
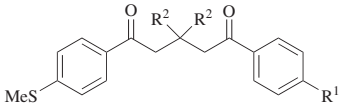
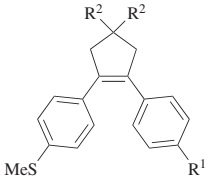
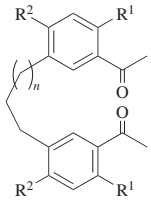
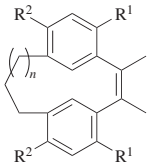
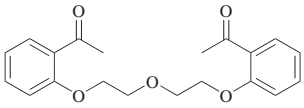
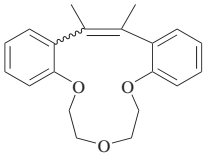
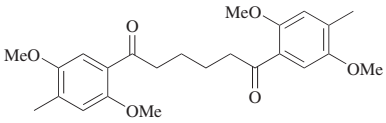
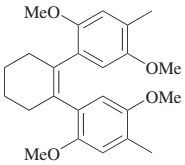
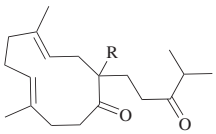
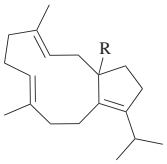
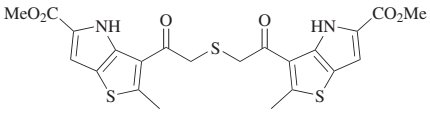
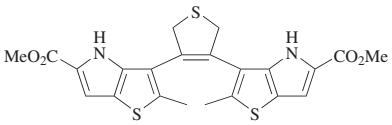
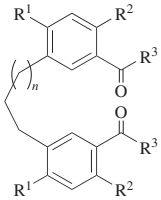
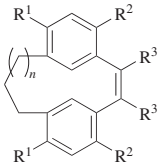
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{19-21}			
	1. $TiCl_4$, Zn, py, THF, reflux, 2 h 2. Reflux, 80 h 3. Reflux, 10–12 h	 R: Me (82); Et (60)	234
	$TiCl_4$, Zn, THF	 R^1 R^2: F Me (—); Cl Me (—); F CF_3 (—); F Et (—)	701
C_{19-22}			
	1. $TiCl_4$, Zn, THF 2. Py, reflux, 60 h 3. Reflux, 8 h	 n R^1 R^2: 1 MeO H (40); 1 H MeO (80); 2 MeO H (69); 2 H MeO (83); 3 H MeO (77); 4 H MeO (19)[b]	621 702, 703 621 702, 703 702, 703 702, 703
C_{20}			
	1. $TiCl_4$, Zn, dioxane, reflux, 1 h 2. Dropwise addition, reflux 3. 16 h	 (81.9), (*E*)/(*Z*) = 41:59	626
	$TiCl_4$, Zn, THF, reflux, 16 h	 (42)	704
	1. $TiCl_3$, Zn/Cu, DME, reflux, time 1 2. Reflux, 12 h 3. Reflux, time 2	 R: t-Bu(Ph)$_2$SiOCH$_2$: Time 1 (h) 6, Time 2 (h) 6, (90) Me: 6, 6, (91) Me: 2, 5, (90)	705 705 250
	1. $TiCl_4$, Zn, THF, heat, 1 h 2. Py, 20° 3. Reflux, 6 h	 (51)	706
C_{21-30}			
	1. $TiCl_4$, Zn, THF 2. Py, reflux, 60 h 3. Reflux, 8 h	 n R^1 R^2 R^3: 1 H Me Me (26.5)[b]; 1 H H Ph (55); 2 MeO H Ph (40)	629 707 707

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

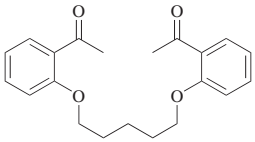
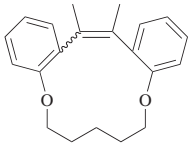
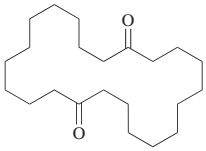
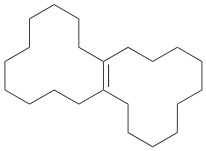
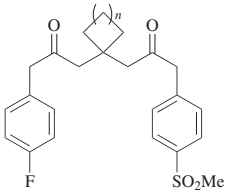
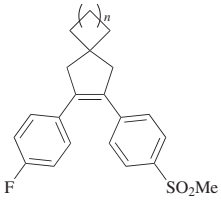
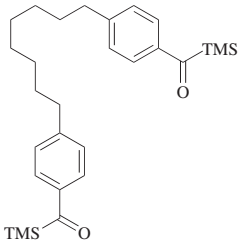
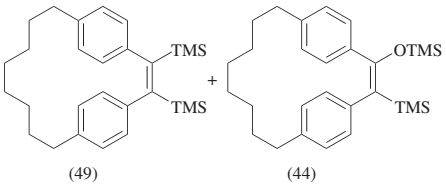
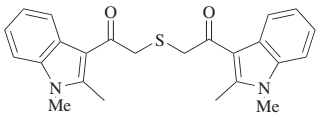
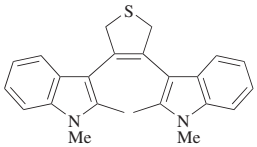
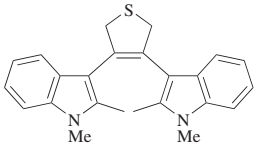
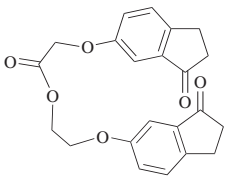
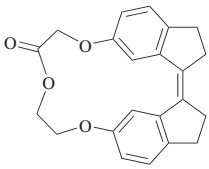
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21} 	1. $TiCl_3$, Zn, dioxane, reflux 2. Reflux, 20 min 3. Reflux, 30 h	 (91), (*E*)/(*Z*) = 24:76	626
C_{22} 	$TiCl_3$, Li	 (62–73)	698
C_{22-24} 	$TiCl_4$, Zn, THF	 *n*: 1 (76); 2 (71); 3 (81)	708
C_{22} 	1. $TiCl_3$, Na/Al_2O_3, DME, reflux, 1 h 2. Reflux, 2 h 3. Reflux, 2.5 h	 (49) + (44)	70
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, 20° 3. Reflux, 6 h	 (18)	688
	1. $TiCl_4$, $NaAlH_4$, THF, 0–2°, 1 h 2. 0–2° 3. rt, 1 h; then 60°, 8 h	 (11)	709
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 3–6 h 3. Reflux, 20–40 min	 (52)	710

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

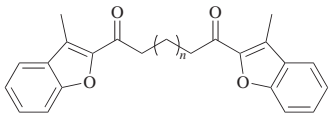
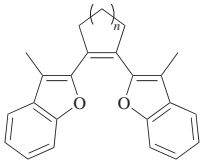
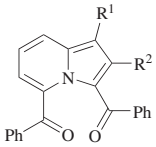
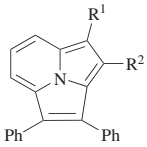
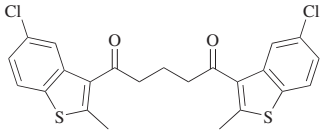
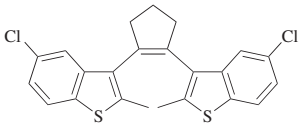
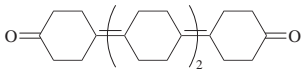
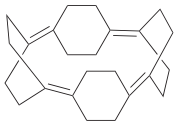
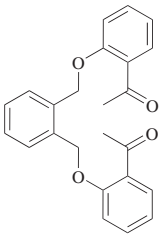
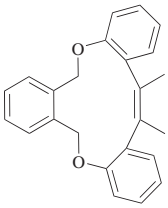
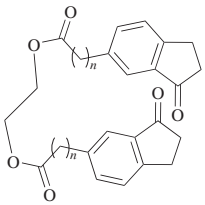
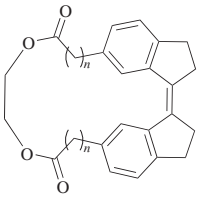
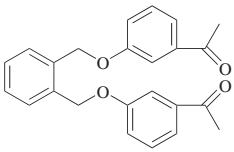
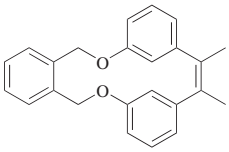
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{23–24}$			
	1. $TiCl_4$, $NaAlH_4$, THF, 0–2°, 1 h 2. Dropwise addition, 0-2° 3. rt, 1 h; then 60°, 4 h	 *n*: 1 (43); 2 (47)	711
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. rt, 40 min 3. rt, 30 min	 R^1 / R^2: NC / H (95); MeO_2C / H (90); EtO_2C / EtO_2C (90)	712
C_{23}			
	$TiCl_4$, Zn, THF, reflux, 30 h	 (53)	713
C_{24}			
	$TiCl_3$, Zn/Cu, DME, reflux, 48 h	 (90)	231
	1. $TiCl_3$, Zn, dioxane, reflux 2. Reflux, 20 min 3. Reflux, 3 h	 (60)	626
$C_{24–26}$			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 3–6 h 3. Reflux, 20–40 min	 *n*: 1 (70); 2 (76)	710
C_{24}			
	1. $TiCl_3$, Zn/Cu, THF, reflux, 1 h 2. Reflux, 8 h 3. Reflux, 13 h	 (78)	637

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

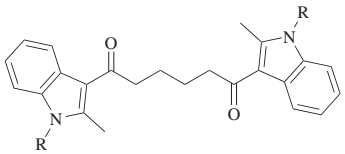
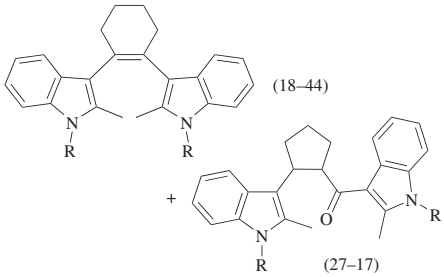
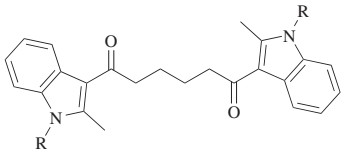
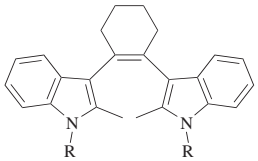
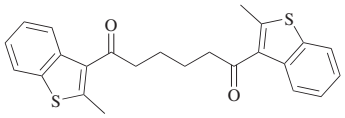
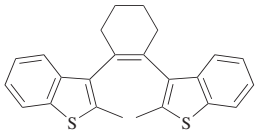
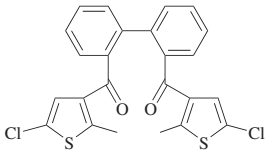
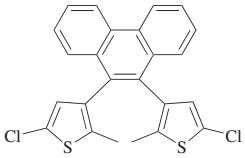
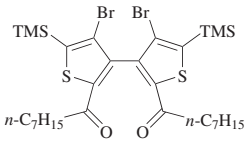
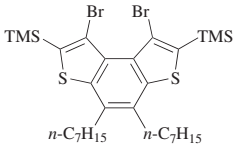
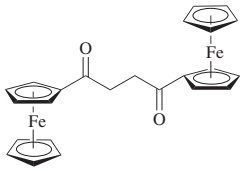
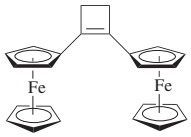
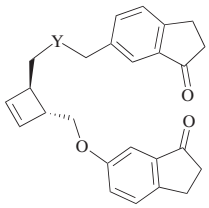
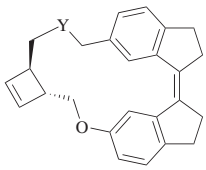
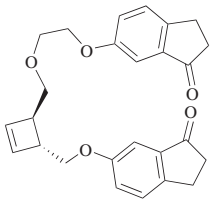
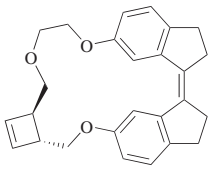
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}			
 R = Me, Et, Bn, n–$C_{16}H_{33}$	$TiCl_4$, Zn, THF, reflux, 20–48 h	 (18–44) (27–17)	714
	1. $TiCl_4$, Zn, THF or dioxane, reflux, 1 h 2. 20° 3. Reflux, 20 h	 R: Et (26); Bn (23); n-$C_{16}H_{33}$ (44)	688
	1. $TiCl_4$, Zn, THF or dioxane, reflux, 1 h 2. 20° 3. Reflux, 20 h	 (40)	688
	$TiCl_4$, Zn, THF, reflux	 (—)	715
	$TiCl_3$, Zn, DME, rt, 1 h; then 85–90°, 20 h	 (77)	716
	$TiCl_4$, Zn, py, THF, rt, 5 h	 (56)	717
C_{25}			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 3–6 h 3. Reflux, 20–40 min	 Y: O (—); S (—)	718
C_{26}			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 3–6 h 3. Reflux, 20–40 min	 (—)	718

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

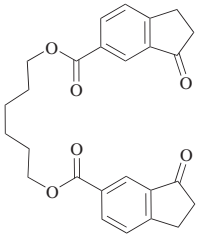
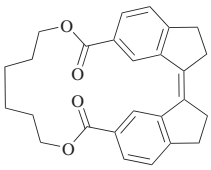
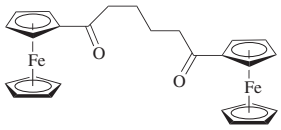
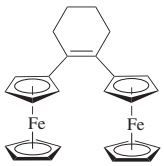
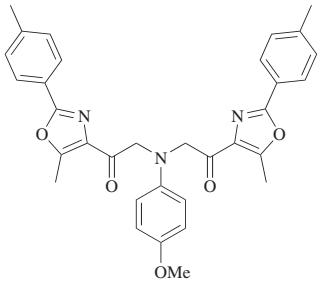
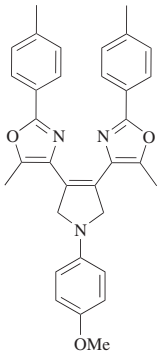
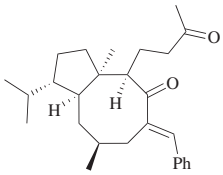
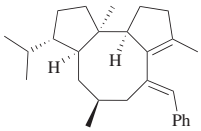
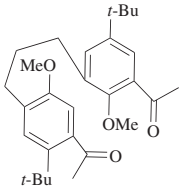
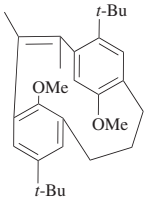
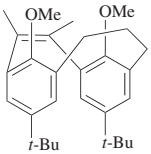
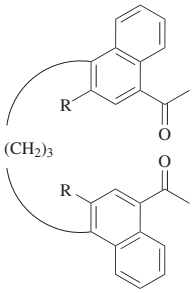
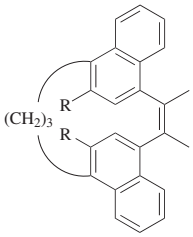
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{26}			
	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. Reflux, 3–6 h 3. Reflux, 20–40 min	 (65)	710
	1. $TiCl_4$, $LiAlH_4$,THF, reflux, 3 h 2. Reflux, 5 h 3. Reflux, 30 min	 (53)	456
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. rt 3. rt, 24 h	 (78)	697
C_{27}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 1.5 h 2. Reflux 3. Reflux, 3.5 h	 (73)	249, 719
	1. $TiCl_4$, Zn, THF 2. Py, reflux, 60 h 3. Reflux, 8 h	 (17) +  (13)	720
C_{27-29}			
	1. $TiCl_4$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 72 h 3. Reflux, 12 h	 R: H (41); Me (50)	150

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

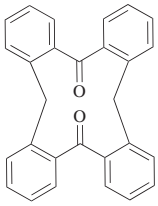
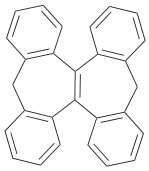
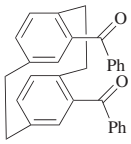
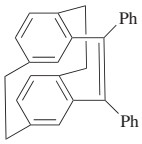
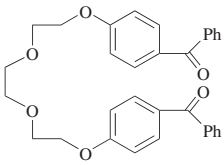
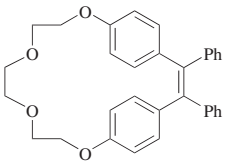
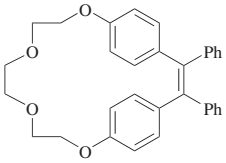
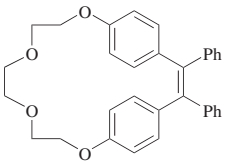
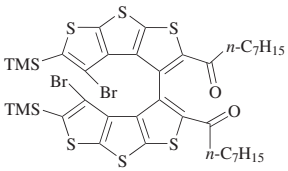
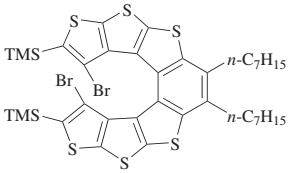
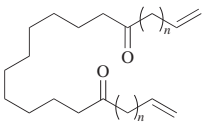
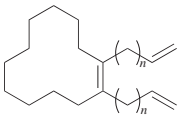
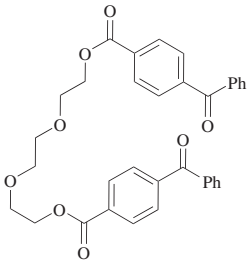
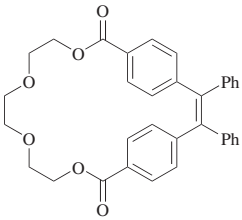
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{28}			
	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux 3. Reflux, 3 d	 (81)	224
C_{30}			
	1. $TiCl_4$, Zn, py, THF 2. 0°, 20 min 3. Reflux, 4 h	 (79)	235
C_{32}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 0.5 h 3. Reflux, 0.5 h	 (81)	69, 85
	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 2 h 3. Reflux, 1 h	 (83)	69, 85
	1. Ti, TMSCl, DME, reflux, 48 h 2. Addition in one lot, reflux 3. Reflux, 8 h	 (57)	69, 85
	$TiCl_3$, Zn, DME, rt, 1 h; then 85–90°, 24 h	 (38)[c]	246
C_{34-38}			
	1. $TiCl_3$, Li, DME, heat 2. 20 h	 n: 9 (78); 11 (82)	659
C_{34}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 30 min 3. Reflux, 30 min	 (40)	85

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

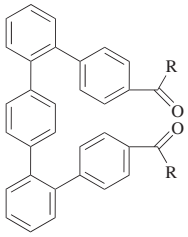
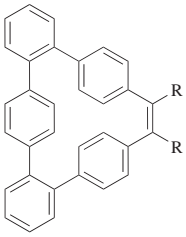
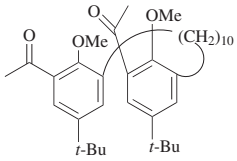
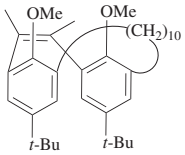
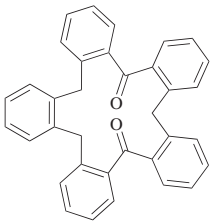
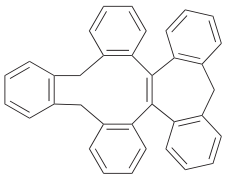
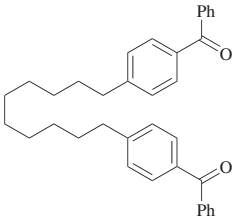
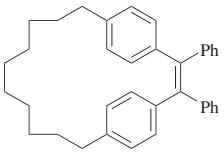
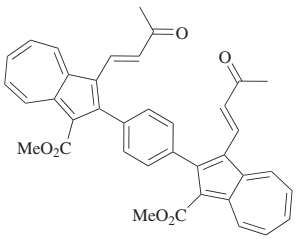
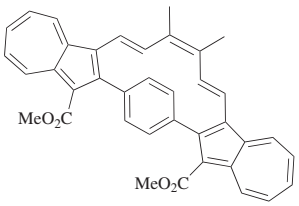
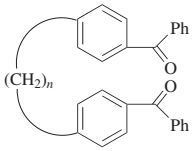
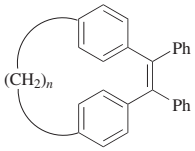
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{34-44} 	1. $TiCl_4$, Zn, THF, py, reflux, 2 h 2. Reflux, 20 h 3. Reflux, 12 h	 R: Me (91); *n*-C_5H_{11} (93); Ph (98); 4-$MeOC_6H_4$ (96)	236
C_{34} 	1. $TiCl_4$, Zn, THF 2. Reflux, 60 h 3. Reflux, 8 h	 (90)	721
C_{35} 	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 20 min 2. Reflux 3. Reflux, 2 d	 (94)	224
C_{36} 	1. $TiCl_3$, M, THF, reflux, time 1 2. Reflux, time 2 3. Reflux, time 3	 (86) M: C_8K, Time 1 (h) 1.5, Time 2 (h) 7, Time 3 (h) 12 M: Na/Al_2O_3, Time 1 (h) 1, Time 2 (h) 2, Time 3 (h) 1	85
	$TiCl_3$, $LiAlH_4$, THF, reflux	 (20)	772
C_{36-52} 	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 2 h 3. Reflux, 2 h	 *n*: 10 (86); 26 (83)	69

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

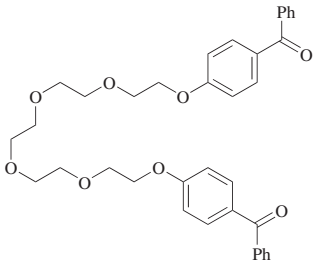
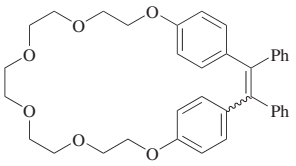
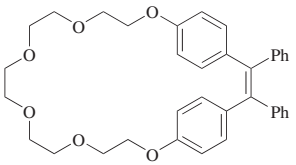
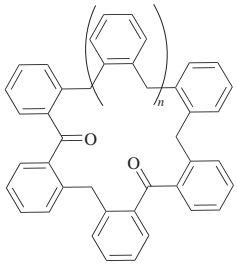
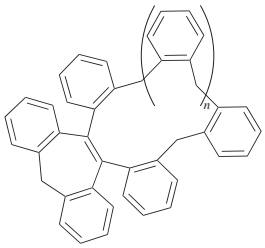
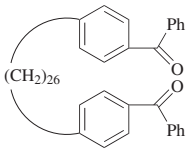
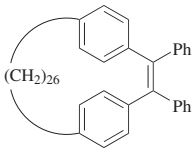
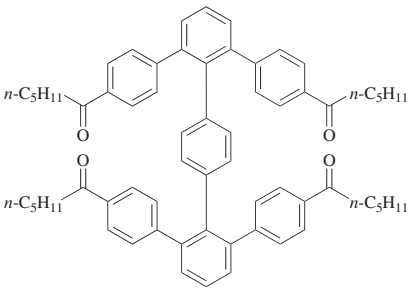
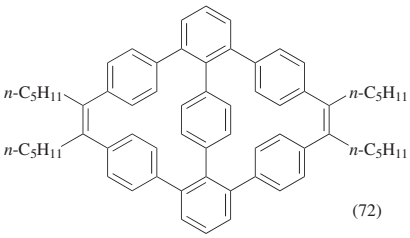
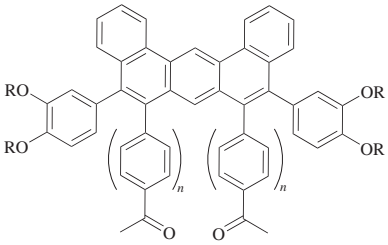
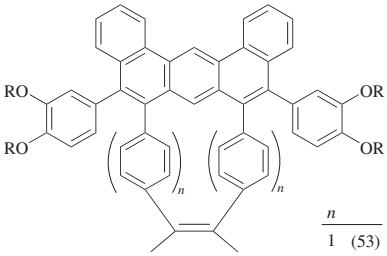
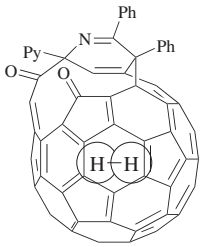
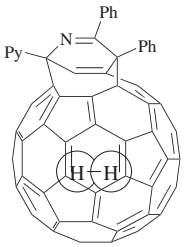
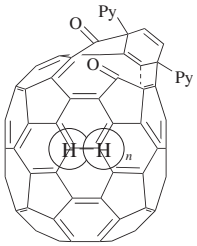
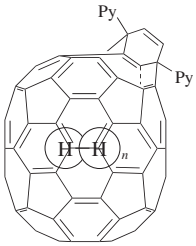
Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{36} 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 30 min 3. Reflux, 30 min	 (63)	85
	1. Ti, TMSCl, DME, reflux, 40 h 2. Addition in one lot, reflux 3. Reflux, 6 h	 (60), (*E*)/(*Z*) = 0:100	85
$C_{42–49}$ 	1. $TiCl_3$, $LiAlH_4$, THF, reflux, 30 min 2. Reflux 3. Reflux, 1 d	 *n*: 1 (92); 2 (87)	723 724
C_{52} 	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Addition in one lot, reflux 3. Reflux, 6 h	 (90)	83
C_{66} 	1. $TiCl_4$, Zn, py, THF, reflux, 2 h 2. Reflux, 4 h 3. Reflux, 12 h	 (72)	725
$C_{48–60}$  R = *n*-C_6H_{13}	1. $TiCl_4$, Zn, THF, 80°, 1 h 2. Py, 80°, 10 h 3. Reflux, overnight	 *n*: 1 (53); 2 (71)	315

TABLE 3B. INTRAMOLECULAR COUPLING OF DIKETONES (*Continued*)

Diketone	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{80} 	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. rt 3. 1,2-dichlorobenzene, 80°, 2 h	 (88)	726, 727 728, 729
C_{82}  (n = 1)/(n = 2) = 97:3	1. $TiCl_4$, Zn, THF, reflux, 1.5 h 2. rt 3. 1,2-dichlorobenzene, 80°, 45 min	 (61)	316

[a] This is produced by the Cope rearrangement of the McMurry product.

[b] This is the yield in the absence of pyridine.

[c] This is the yield of *rac*-**II** from *rac*-I. (*M*)-**II** (er 87.0:13.0) and (*P*)-**II** (er 75.0:25.0–95.0:5.0) were obtained from (*R*)-**I** (er 78.0:22.0) and (*S*)-I (er 85.5:14.5–95.5:4.5) in 28 and 17–63% yields, respectively.

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES

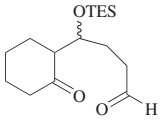
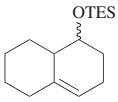
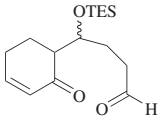
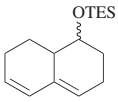
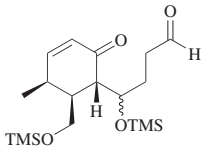
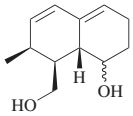
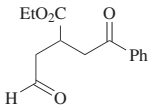
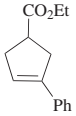
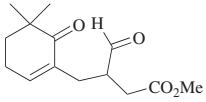
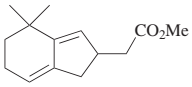
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} 	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 30 h	 (64)	84, 679
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 3 h	 (82)	84, 679
C_{12} 	$TiCl_3$, Zn/Cu, DME, reflux	 (72) dr 1.3:1	730
	1. $TiCl_4$, Zn, py, THF, rt, 1.5 h 2. rt 3. Reflux, overnight	 (64)	731
C_{13} 	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 97 h	 (52)	247

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

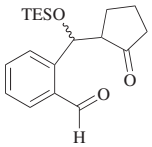
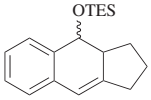
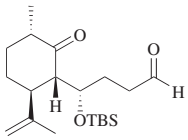
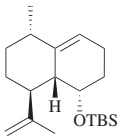
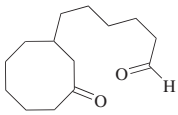
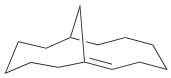
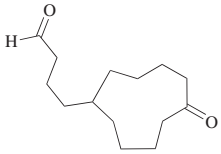
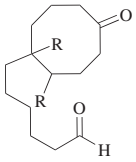
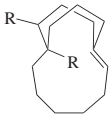
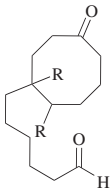
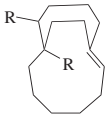
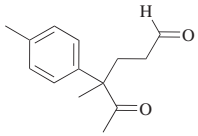
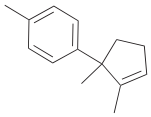
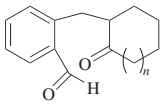
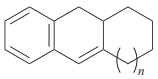
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13}			
	1. $TiCl_3$, C_8K, dioxane, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 30 h	 Isomer (*R**,*S**) (64) (*R**,*R**) (67)	84, 679
C_{14}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, reflux 2. Reflux, 12 h	 (60)	732
	1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 24 h 3. Reflux, 2 h	 (38)	733
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 35 h	 (30)	734, 735
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 35 h	 R H (35) D (—)	220
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 40 h	 R H (36) D (—)	220
	1. $TiCl_3$, K, THF, reflux, 45 min 2. Reflux 3. Reflux, 12 h	 (55)	62
$C_{14–15}$			
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 10 h 3. Reflux, 11–14 h	 *n* 1 (81) 2 (86)	84, 679

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

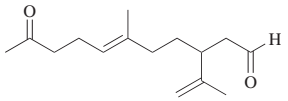
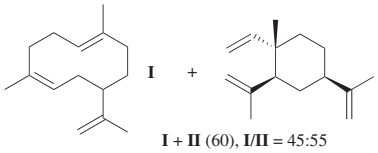
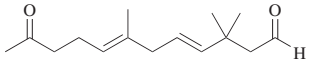
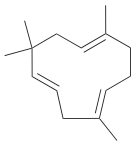
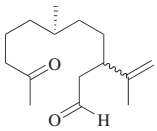
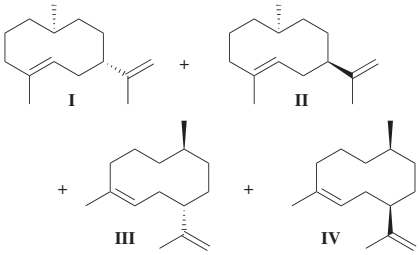
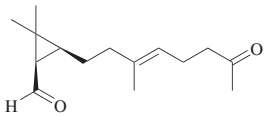
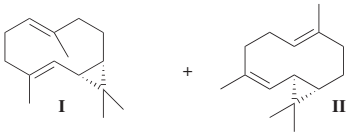
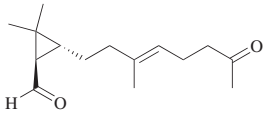
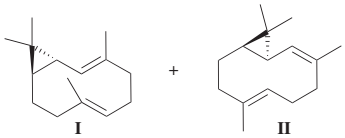
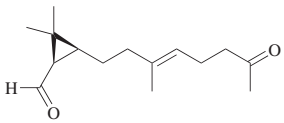
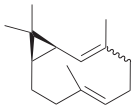
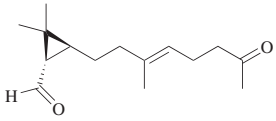
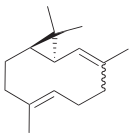
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}			
	$TiCl_3$, Zn/Cu, DME, reflux, 34 h	 **I** + **II** (60), **I/II** = 45:55	268
	$TiCl_3$, Zn/Cu, DME, reflux, 18 h	 (60)	270
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. Reflux, 30 h 3. Reflux, 5 h	 **I** + **II** + **III** + **IV** (45), **I/II/III/IV** = 1.0:1.1:1.6:2.0	267
	1. $TiCl_3$, Zn/Cu, DME, reflux, 7 h 2. Reflux, 42 h 3. Reflux, 2 h	 **I** + **II** (60), **I**:**II** = 3:1	266
	1. $TiCl_3$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 46 h 3. Reflux, 2.5 h	 **I** + **II** (78), **I/II** = 2:3	266
	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 30 h	 (61), (*E*)/(*Z*) = 80:20	265
	1. $TiCl_3$, Zn/Cu, DME 2. Reflux, 30 h	 (75), (*E*)/(*Z*) = 40:60	265

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

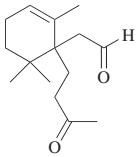
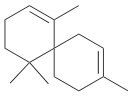
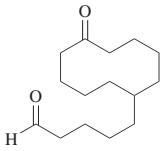
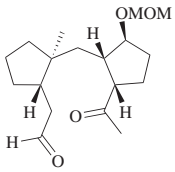
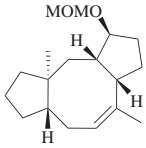
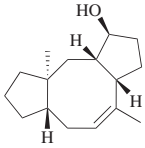
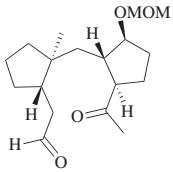
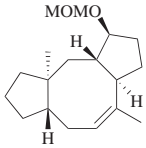
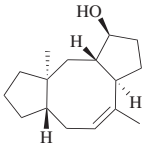
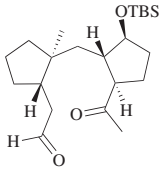
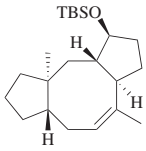
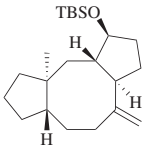
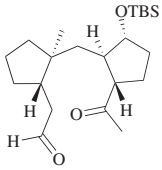
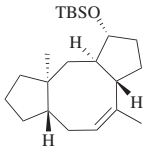
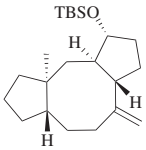
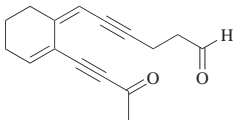
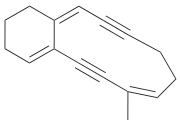
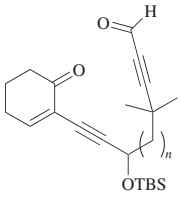
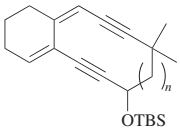
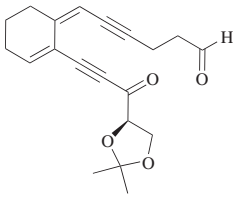
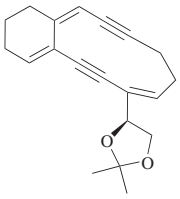
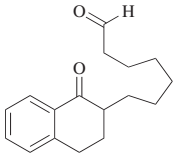
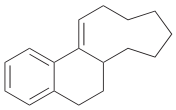
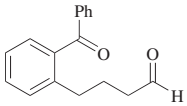
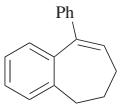
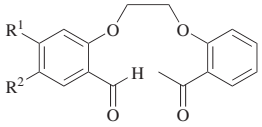
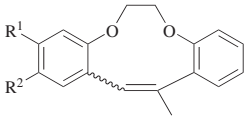
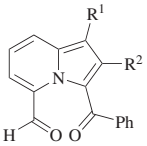
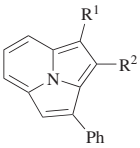
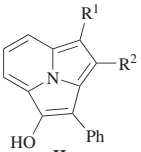
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 25 h 3. Reflux, 14 h	 (45)	254
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 35 h	(22)	220
C_{16}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 3 h 2. Reflux, 21 h 3. Reflux, 12 h	 (29) +  (16)	263
	1. $TiCl_3$, Zn/Cu, DME, reflux, 6 h 2. Reflux, 40 h 3. Reflux, 2.5 h	 (18) +  (31)	263
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 10 h 2. Reflux, 12 h 3. Reflux, 2 h	 (31) +  (29)	264
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 10 h 2. Reflux, 12 h 3. Reflux, 2 h	 (40) +  (29)	264
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. –5°, 6 h 3. –5°, 15 h	 (47)	228
C_{16-17}			
	1. $TiCl_3(DME)_2$, Zn/Cu, DME, reflux, 3 h 2. rt, 14 h 3. rt, 1 h	 *n*: 1 (41); 2 (18)	736

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 5 h 2. 30–35°, 3 h 3. 30–35°, 1.5 h	 (>45)[a]	737, 228
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 16 h 3. Reflux, 12 h	 (31.2)	738
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9 h 3. Reflux, 12 h	 (80)	61, 27
C_{17-19}			
	1. $TiCl_4$, Zn, solvent, reflux, 2.5 h 2. rt 3. Reflux, time		

R^1	R^2	Solvent	Time (h)		(*E*)/(*Z*)	
H	H	THF	20	(25)	2:1	619
H	H	DME	16	(41)	45:55	618
Me	MeO	THF	1.5	(70)	1:3	619

C_{17-18}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. rt, 40 min 3. rt, 30 min	 **I** +  **II**	712

R^1	R^2	**I**	**II**
NC	H	(30)	(29)
MeO_2C	H	(38)	(41)
EtO_2C	EtO_2C	(20)	(55)

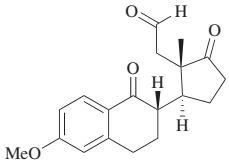
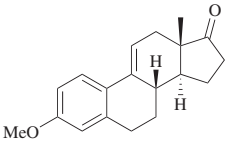
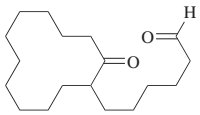
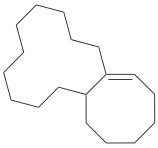
C_{18}			
	1. $TiCl_3$, Zn/Ag, DME, reflux, 2 h 2. Reflux 3. Reflux, 2 h	 (56)[b]	257, 739 258, 740
	1. $TiCl_3$, Zn/Cu, DME, reflux, 4.6 h 2. Reflux, 25.5 h 3. Reflux, 5.8 h	 (—)	741

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

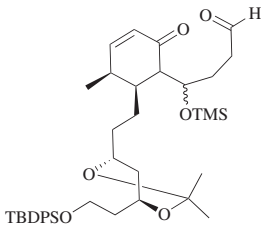
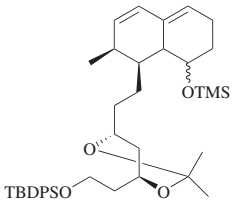
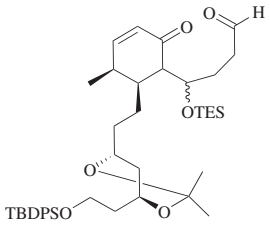
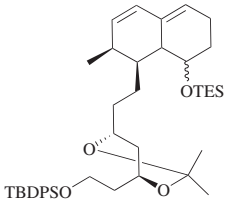
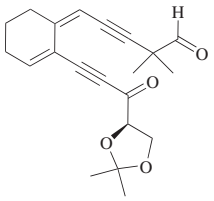
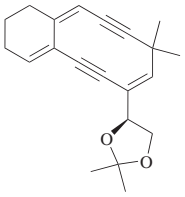
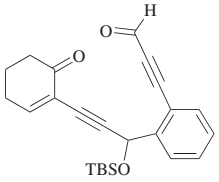
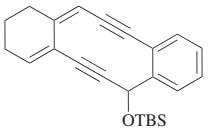
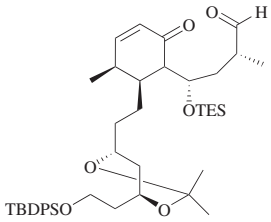
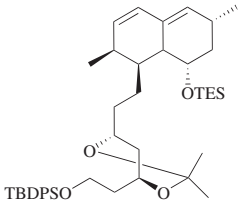
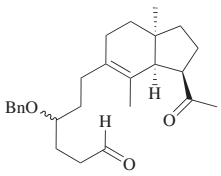
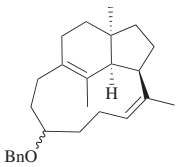
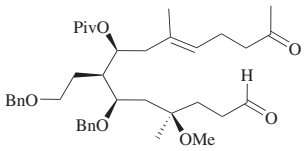
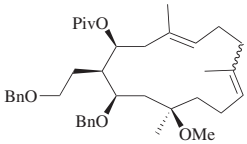
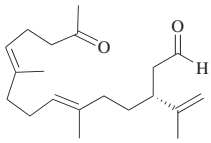
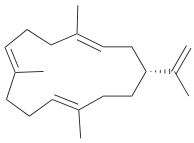
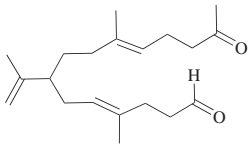
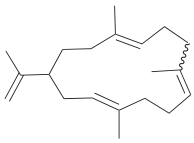
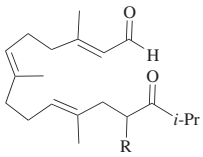
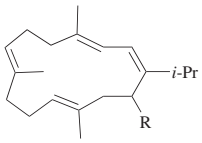
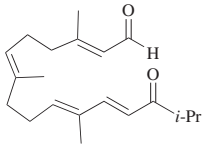
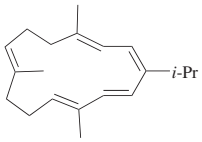
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}			
	$TiCl_4$, Na, naphthalene, THF	 (71)	84
	1. $TiCl_3$, C_8K, DME 2. 9 h 3. rt, 15 h; then reflux, 3 h	 (85)	251
	1. $TiCl_3(DME)_2$, Zn/Cu, DME, reflux, 5 h 2. 35°, 3 h	 (42)	742
	1. $TiCl_3$, Zn/Cu, DME, reflux, 6 h 2. 30°, 4 h	 (17)	742a
C_{19}			
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. rt, 9 h 3. rt, 14 h; then reflux, 4 h	 (86)[b]	75, 251
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux 2. Reflux, "several hours"	 (11)	269

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{19}			
	$TiCl_3$, Zn/Cu, DME, reflux	 (65), (*E*)/(*Z*) = 4:3	286
C_{20}			
	1. $TiCl_4$, Zn, DME, reflux, 1.5 h 2. Reflux, 30 h 3. Reflux, 3 h	 (81)	278, 743
	1.$TiCl_3$, $AlCl_3$, Zn/Cu, DME, reflux, 3.5 h 2. Reflux, 30 h 3. Reflux, 6 h	 (82), (*E*)/(*Z*) >96:<4	273
	1. $TiCl_3$/$AlCl_3$, Zn/Cu, solvent, reflux, time 1 2. Reflux, time 2 3. Reflux, time 3		

R	Solvent	Time 1 (h)	Time 2 (h)	Time 3 (h)		Refs.
H	DME	1.5	36	3	(40)	274
BnO	THF	3	28	5	(62)	285

	1. $TiCl_4$, Zn, py, solvent, reflux, 2 h 2. Reflux, time 3. Reflux, 3 h		

Solvent	Time (h)		Refs.
THF	17	(82)	275
DME	13	(72)	276

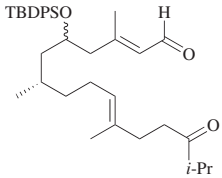
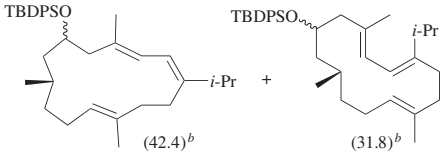
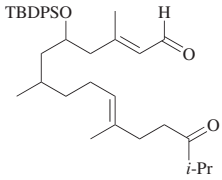
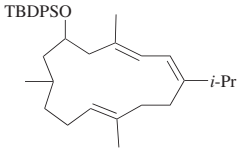
	1. $TiCl_4$(DME), Zn, py, DME, reflux, 2.5 h 2. Reflux, 20 h 3. Reflux, 3 h	 (42.4)[b] + (31.8)[b]	744
	$TiCl_4$, Zn, py, DME, reflux, 30 h	 (62)	287

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

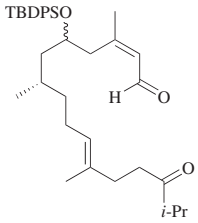
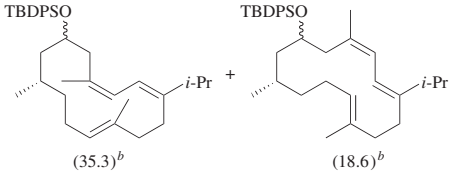
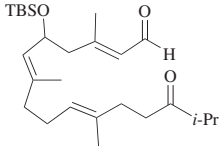
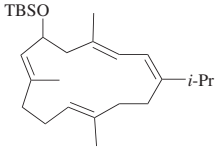
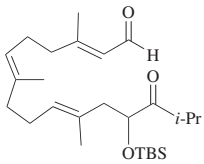
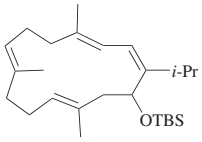
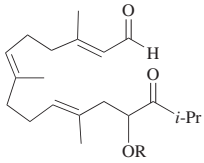
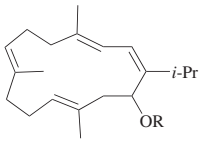
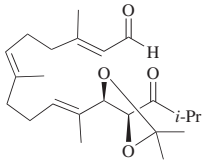
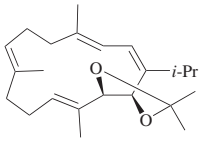
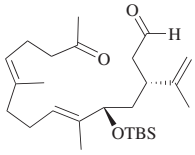
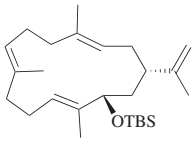
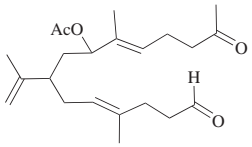
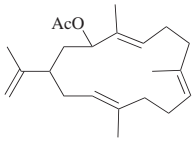
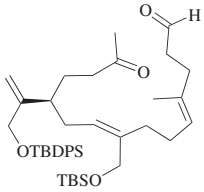
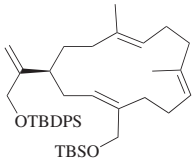
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	1. $TiCl_4$(DME), Zn, py, DME, reflux, 2.5 h 2. Reflux, 20 h 3. Reflux, 3 h	 (35.3)[b] + (18.6)[b]	744
	1. $TiCl_4$(DME), Zn, py, DME, reflux, 2.5 h 2. Reflux, 24 h 3. Reflux, 3 h	 (66)	288, 745
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 20 h	 (62)	284
	1. $TiCl_4$(THF), Zn, py, THF, reflux, 2.5 h 2. Reflux, 26 h 3. Reflux, 4 h	 R: TBS (78); TBDPS (78)	746, 280
	1. $TiCl_4$, Zn, py, THF 2. Reflux, 20 h	 (58)	284
	1. $TiCl_4$, Zn, py, DME, reflux, 2 h 2. Reflux, 8 h 3. Reflux, 2 h	 (81)[b]	281, 283
	1. $TiCl_4$, Zn/Cu, THF, reflux, 2 h 2. Reflux, 30 h 3. Reflux, 3 h	 (38)	282
	$TiCl_4$, Zn, py, DME, reflux	 (69)[b]	289

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

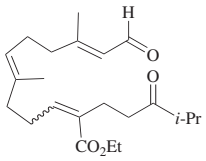
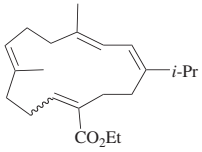
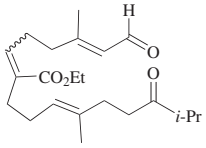
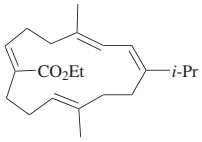
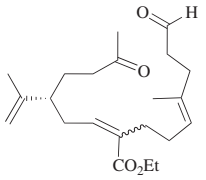
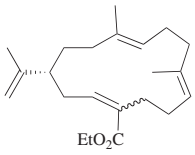
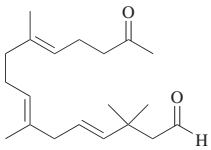
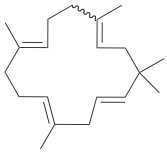
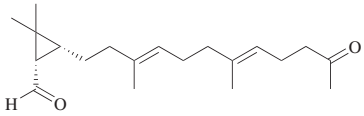
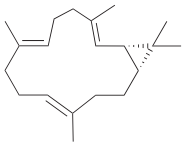
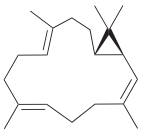
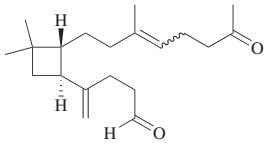
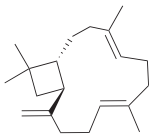
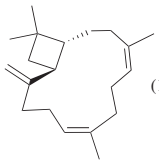
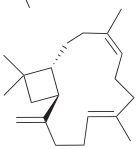
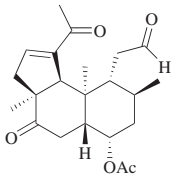
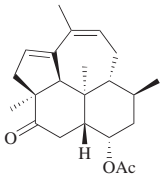
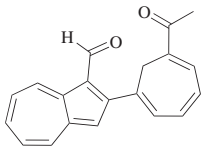
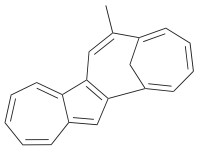
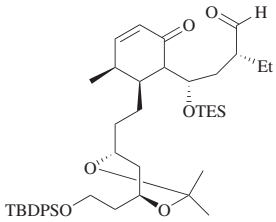
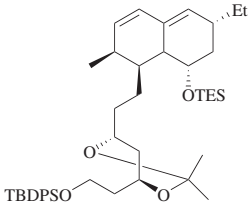
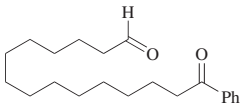
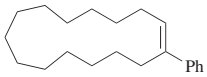
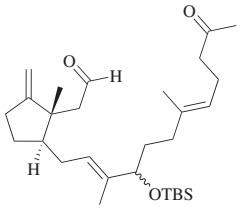
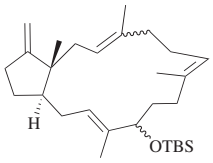
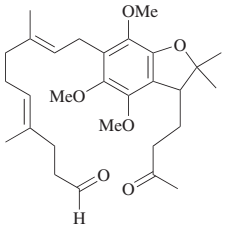
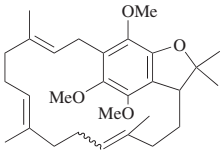
Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 6 h 3. Reflux, 2 h	 (48), (*E*)/(*Z*) = 1:1	279, 747
	1. $TiCl_4$, Zn, THF, reflux, 2 h 2. Reflux, 6 h 3. Reflux, 2 h	 (42)	747
	1. $TiCl_3$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 6 h 3. Reflux, 2 h	 (41)[b], (*E*)/(*Z*) = 1:2	277
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 32 h 3. Reflux, 8 h	 (79), (*E*)/(*Z*) = 2:1	290, 291
	1. $TiCl_3$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 38 h 3. Reflux, 3 h	 +  **I** **II** **I** + **II** (75)[b], **I**/**II** = 2:1	266
 (*E*)/(*Z*) = 5:11	1. $TiCl_3$, Zn/Cu, DME, reflux, 17 h 2. Reflux, 4 d 3. Reflux, 4 h	 (16) +  (17) +  (19)	748
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME, reflux, 4 h 2. Reflux, 12 h 3. Reflux, 2 h	 (32)	260

TABLE 3C. INTRAMOLECULAR COUPLING OF KETO ALDEHYDES (*Continued*)

Keto Aldehyde	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	$TiCl_3$, $LiAlH_4$, DME, reflux, 8 h	 (3–5)	630
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. rt, 9 h; then reflux, 5 h 3. rt, 5 h	 (89)[b]	749
C_{21}			
	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 9 h 3. Reflux, 12 h	 (80)	61, 27
C_{23}			
	1. $TiCl_3$, Zn/Cu, DME, 80° 2. 80°, 24 h	 (54), (*E*)/(*Z*) = 64:36	292
C_{26}			
	1. $TiCl_3$, C_8K, DME, reflux, 2 h 2. Reflux, 20 h 3. Reflux, 3 h	 (11)	293

[a] The product was isolated after acetonide deprotection.

[b] Optically active starting material was employed.

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS

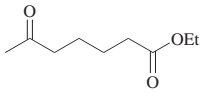
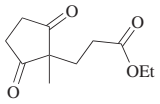
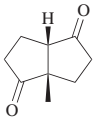
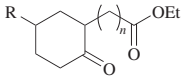
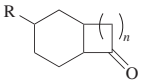
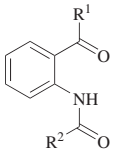
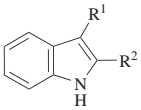
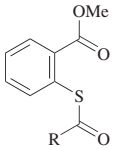
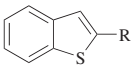
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h 3. Reflux, 6 h	(77)[a]	73, 74 79
C_9			
	$TiCl_3(DME)_{1.5}$, Zn/Cu, DME, heat	 (18)[a]	750
C_{9-18}			
	1. $TiCl_3$, $LiAlH_4$, Et_3N, DME, reflux, 1.5 h 2. Reflux, 24 h 3. Reflux, 3 h	 R, n *t*-Bu, 1, (57)[a] H, 2, (75)[a] H, 3, (80)[a] H, 4, (82)[a] H, 5, (52)[a] H, 7, (50)[a] H, 11, (54)[a]	63
C_{9-29}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, time 1 3. Reflux, time 2	 R^1, R^2, Time 1 (h), Time 2 (h) Me, H, 0, 3, (69) Me, Me, 8, 0, (70) H, Ph, 0, 2, (90) Ph, H, 8, 0, (92) Me, Ph, 8, 0, (75) Ph, Me, 8, 0, (87) Ph, *t*-Bu, 0, 3, (84) Ph, 2-C_4H_3S, 0, 2, (79) Ph, Ph, 8, 0, (90) Ph, n-$C_{15}H_{32}$, 3, 0, (92)	79, 78
C_{9-15}			
	1. $TiCl_4$, Zn, $LiAlH_4$, CH_2Cl_2, rt, 1 h 2. rt 3. Reflux, time	 R, Time (h) Me, 1, (70) 2-C_4H_3O, 0.25, (85) 2-C_4H_3S, 5, (85) 3-C_5H_4N, 1, (60) Ph, 2, (87) 4-ClC_6H_4, 0.25, (80) 2,4-$Cl_2C_6H_3$, 0.5, (80) 2-$MeOC_6H_4$, 2, (80) n-C_7H_{15}, 4, (65) Bn, 5, (85) 4-MeC_6H_4, 0.5, (75)	133

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

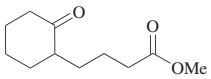
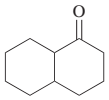
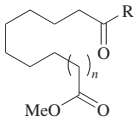
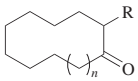
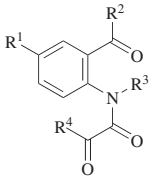
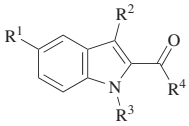
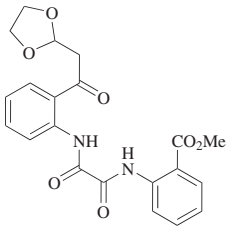
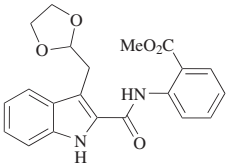
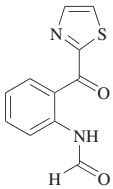
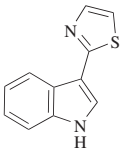
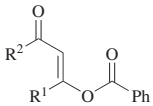
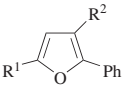
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h 3. Reflux, 6 h	 (91)[a]	73, 74 79
$C_{11–14}$			
	1. $TiCl_3$, $LiAlH_4$, Et_3N, DME, reflux, 1.5 h 2. Reflux, 24 h 3. Reflux, 3 h	 R, *n*: Me, 1, (50)[a]; Et, 2, (45)[a]; Et, 3, (63)[a]; Me, 4, (60)[a]	63
$C_{11–15}$			
	Ti/graphite, DME, reflux, 0.5–1 h	 R^1, R^2, R^3, R^4: H, Me, H, Me, (60); Cl, Ph, H, EtO, (93); Cl, Ph, Me, EtO, (94)	80
C_{11}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. 0° 3. 0°, 21 h; then reflux, 5 h	 (—)	751
	$TiCl_3$, Zn, DME, reflux, 20 min	 (71)	752, 471
$C_{12–22}$			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h	 R^1, R^2: Me, Me, (58); Ph, Ph, (92)	79, 78

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

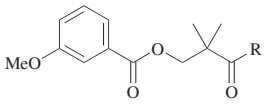
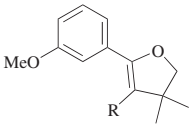
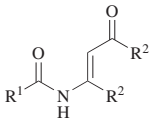
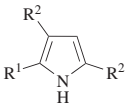
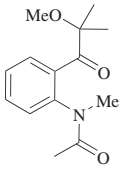
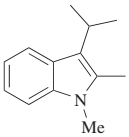
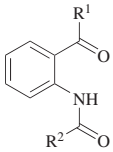
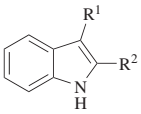
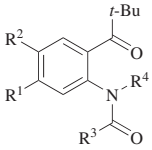
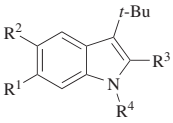
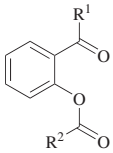
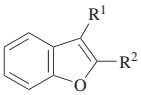
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-16} 	—	 R: H (—); Me (—); *i*-Pr (—); *t*-Bu (—)	753
C_{12-26} 	$TiCl_3$, Zn, THF, reflux	 R^1 R^2 Time (h): Ph Ph 3 (78); *t*-Bu Ph 0.5 (60); *n*-C_3F_7 Ph 2 (54); 2-Np Ph 1 (77); Ph Me 3 (38)	754
C_{12} 	$TiCl_3$, Zn, DME, reflux, 1 h	 (54)	755
C_{13-23} 	$TiCl_3$, Zn, DME, reflux	 R^1 R^2 Time (h): EtO_2C *t*-Bu 2 (58); *c*-C_3H_5 Ph 96 (78); 2-C_4H_3N Ph 4 (58); Ph 15 (57); *n*-C_9H_{19} Ph 72 (73); Ph Ph—≡—≀– 0.8 (77)	751
C_{13-19} 	$TiCl_3$, Zn, DME, reflux, 1 h	 R^1 R^2 R^3 R^4: H Cl Me Me (77); MeO_2C H Ph Me (81); H H Ph Me (82); H H Me Bn (68)	755
C_{14-20} 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h	 R^1 R^2: H Ph (89); Ph Me (85); Me Ph (80); Ph Ph (88)	78, 79

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

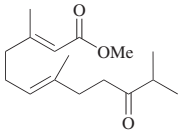
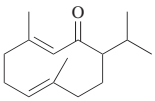
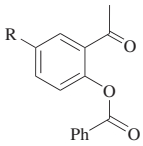
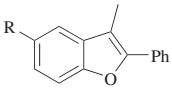
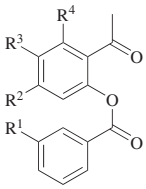
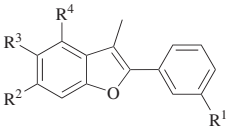
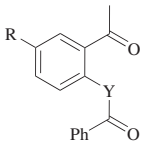
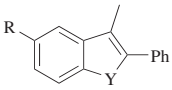
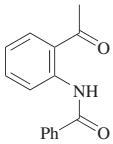
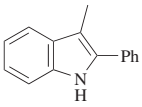
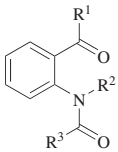
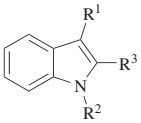
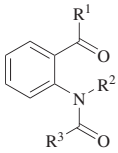
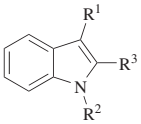
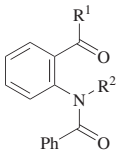
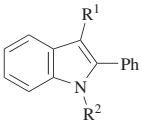
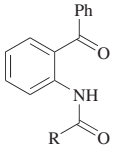
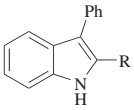
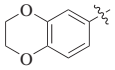
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15}			
	1. $TiCl_4$, $LiAlH_4$, Et_3N, DME, reflux, 2 h 2. Reflux, 20 h 3. Reflux, 4 h	 (62)	756, 322
	1. $TiCl_3$, Li, THF, reflux, 3 h; then I_2, 5 min 2. rt 3. rt, 8 h	 R: H (62); MeO (55)	115
	$TiCl_4$, Zn, dioxane, reflux, 6 h	 R^1 R^2 R^3 R^4: H H H H (55); MeO H H H (60); H MeO H H (58); H H MeO H (56); H H H MeO (45); H H MeO MeO (24)	757
	1. $TiCl_3$, Li, naphthalene, THF, reflux, 3 h 2. rt 3. rt, 14 h	 R Y: H O (55); MeO O (52); H HN (60)	67
	1. Ti powder, $(i\text{-PrO})_3TiCl$, TMSCl, DME, reflux, 68 h 2. Addition in one lot, reflux 3. Reflux, 2.5 h	 (97)	83
C_{15-18}			
	1. $TiCl_3$, C_8K, reflux, DME, 1.5 h 2. Addition in one lot, reflux 3. Reflux, time	 R^1 R^2 R^3 Time (h): Me H Ph — (75); Me Me Ph 0.5 (92); *t*-Bu Me Ph 3 (62); *t*-Bu Me *i*-Pr 22 (36); *t*-Bu Me *t*-Bu 1 (35)	7
C_{15-21}			
	$TiCl_3$, Zn, DME, reflux	 R^1 R^2 R^3 Time (h): Me H Ph 0.75 (76); *n*-Bu Me Ph 4 (70); *t*-Bu H Ph 69 (86); *t*-Bu Me Ph 4 (75); *t*-Bu Me mesityl 67 (88); Bn H Ph 22 (88); Bn H *t*-Bu 92 (95)	7

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-18} 	$TiCl_3$ (8 mol %), Zn, $Me_2ClSi(CH_2)_3CN$, DME, reflux, 30 min	 R^1 R^2: Me H (82); Bu Me (67)	83
C_{15-29} 	$TiCl_3$, Zn, reflux	 R: Ph (DME, 1.5, (98)); n-$C_{15}H_{31}$ (DME, 1.25, (93)); $H_2C{=}CH(CH_2)_8$ (THF, 2, (85)); $ClCH_2(CH_2)_3$ (THF, 2, (86)); CF_3 (THF, 4, (82)); $HO_2C(CH_2)_2$ (THF, 1.5, (51)); c-C_3H_5 (THF, 3, (84)); 2-BrC_6H_4 (DME, 5, (88)); 2-IC_6H_4 (THF, 2.5, (85)); 2-C_4H_3O (THF, 7, (78)); 2-Py (DME, 1, (63)); 2-benzofuranyl (THF, 3, (94)); t-Bu (DME, 2, (97));  (THF, 4, (99))	7

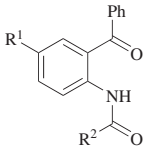
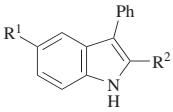
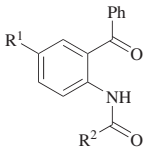
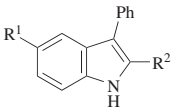
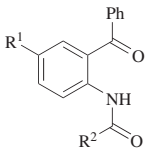
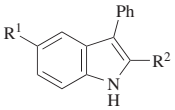
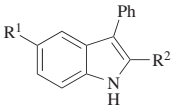
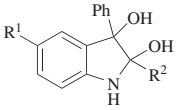
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-20} 	1. $TiCl_3$, Na/Al_2O_3, THF, reflux, 1 h 2. Reflux, 2 h 3. Reflux, 1 h	 R^1 R^2: H Ph (75); Cl EtO_2C (72)	69
C_{15-29} 	$TiCl_3$ (10 mol %), Zn, TMSCl, MeCN, reflux, 30 min	 R^1 R^2: H Ph (80); H CF_3 (88); H n-C_3F_7 (73); Cl EtO_2C (79); H n-$C_{15}H_{31}$ (77); H (69)	83

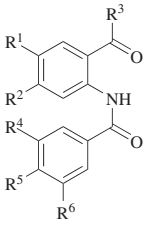
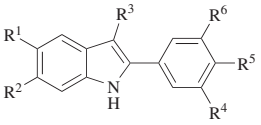
TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-21}			
	1. $TiCl_4$, Sm, THF, reflux, 2h 2. rt 3. Reflux, 1 h		758a

R^1	R^2	
H	Ph	(89)
H	4-MeC_6H_4	(91)
H	4-FC_6H_4	(94)
H	Me	(83)
H	Et	(81)
Cl	Ph	(90)
Cl	4-MeC_6H_4	(86)
Cl	4-ClC_6H_4	(83)
Cl	4-FC_6H_4	(88)
Cl	Me	(78)

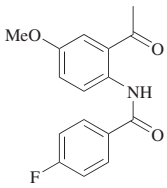
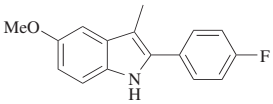
	SmI_2, THF, 65°	 +  **I** **II**	758

R^1	R^2	Time (min)	**I**	**II**
H	Ph	30	(85)	(0)
H	4-MeC_6H_4	30	(84)	(0)
H	4-ClC_6H_4	50	(88)	(0)
Cl	Ph	30	(88)	(0)
Cl	4-MeC_6H_4	30	(84)	(0)
Cl	4-ClC_6H_4	40	(87)	(0)
Cl	4-FC_6H_4	50	(85)	(0)
H	Et	60	(40)	(32)
H	Me	60	(38)	(35)
Cl	Et	60	(43)	(32)
Cl	Me	60	(43)	(30)

	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Reflux 3. Reflux, time		82

R^1	R^2	R^3	R^4	R^5	R^6	Time (h)	
MeO	MeO	Me	H	MeO	H	~2	(66)
H	Me	Ph	H	MeO	H	8	(79)
MeO	MeO	Me	MeO	H	MeO	0.5	(86)

C_{15}

	1. $TiCl_3$, C_8K, DME, heat, 1.5 h 2. Heat 3. Heat, 1 h	 (96)	82

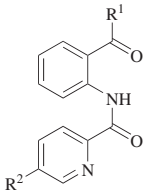
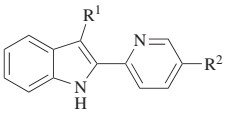
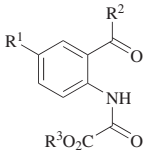
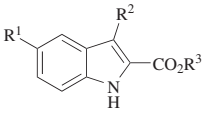
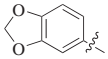
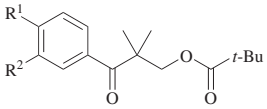
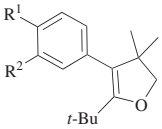
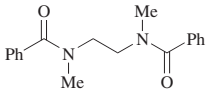
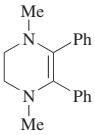
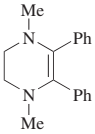
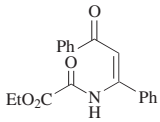
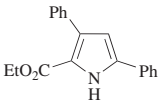
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-17}			
	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, time 1 3. Reflux, time 2		
		R^1 / R^2 / Time 1 (h) / Time 2 (h)	
		$MeO(CH_2)_2$ / H / 3 / 1 (62)	752
		$MeO(CH_2)_2$ / Et / 3 / 1 (52)	752
		/ H / 3.5 / 3 (57)	751
C_{15}			
	$TiCl_3$, Zn, DME, reflux		
		R^1 / R^2 / R^3 / Time	
		Cl / Ph / Et / 2 h (78–81)	471
		H /  / Me / 80 min (73–85)	751
C_{16}			
	1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 30 min 2. Reflux, 1 h 3. Reflux, 1 h		
		R^1 / R^2	
		H / MeO (75.4)	759
		MeO / H (79.0)	
	Sm, SmI_2, THF, 67°, 2–4 h	 (62)	105, 760
	1. Yb, ICH_2CH_2I, THF, 67°, 1 h 2. 67°, 4 h	 (23)	108
C_{17}			
	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Reflux 3. Reflux, 15 min	 (60)	754

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

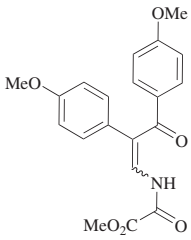
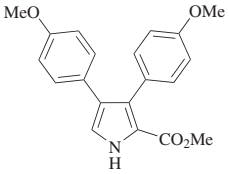
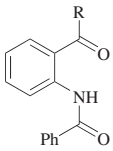
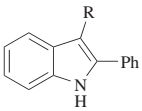
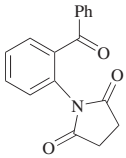
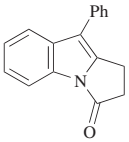
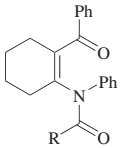
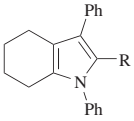
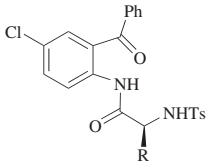
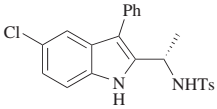
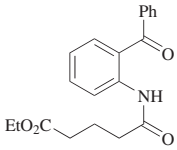
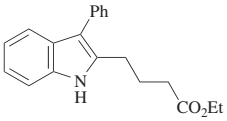
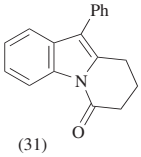
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17} 	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Reflux, 2.5 h 3. Reflux, 15 min	 (52)	754
C_{17-18} 	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Reflux 3. Reflux, time	 R: c-C_3H_5, Time (h): 48, (70) R: 2-C_4H_3N, Time (h): 1, (92)	751
C_{17} 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 3 h	 (61)	79
C_{18-20} 	$TiCl_3$, Zn, THF, reflux	 R: Ph, Time (min): 15, (85) R: t-Bu, Time (min): 30, (58)	754
C_{18-22} 	$TiCl_3$, Zn, TMSCl, MeCN	 R: i-Pr (46) R: Bn (48)	761
C_{18} 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h	 (63) +  (31)	79

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

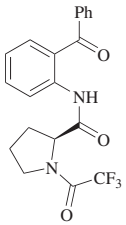
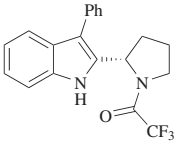
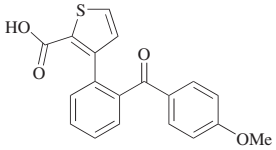
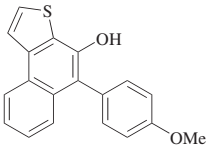
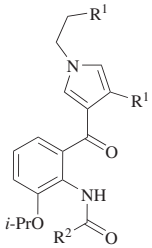
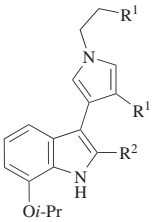
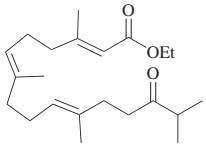
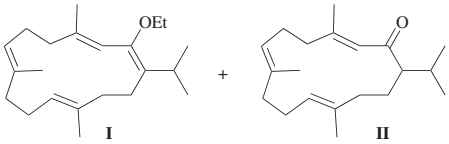
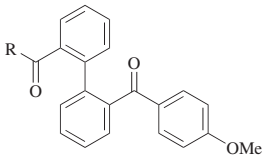
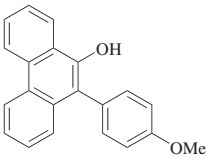
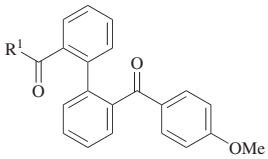
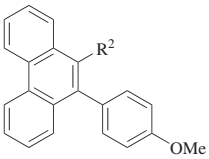
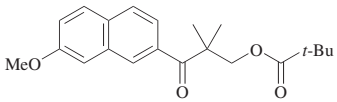
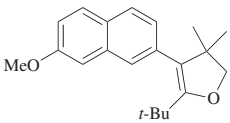
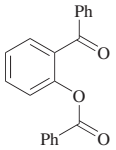
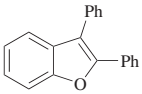
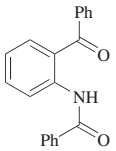
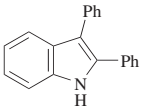
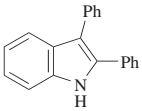
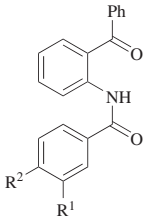
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}			
	$TiCl_3$, Zn, THF, reflux, 1 h	 (90)	7
	$TiCl_3$, Zn, DME, reflux	 (85)	137
$C_{19–26}$			
 $R^1 = 4\text{-}MeOC_6H_4$	$TiCl_3$, C_8K, DME, reflux	 R^2: Me (77); 4-$MeOC_6H_4$ (89); 4-$MeOC_6H_4(CH_2)_2$ (20); 4-$MeOC_6H_4CH{=}CH$ (73)	137
C_{20}			
	1. $TiCl_3$, $LiAlH_4$, DME 2. Et_3N, reflux, 24 h	 **I** + **II** (81), **I/II** = 4:1	762
	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Reflux 3. Reflux	 R: HO (89); F (85)	137
	$TiCl_3$, Zn, DME, reflux	 R^1, R^2: HO, HO (86); F, HO (90); H_2N, H_2N (58)	137
	1. $TiCl_3$, $LiAlH_4$, Et_3N, THF, reflux, 30 min 2. Reflux, 1 h 3. Reflux, 1 h	 (66.3)	759

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

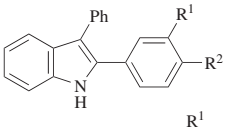
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	$TiCl_3$, Zn, DME, reflux, 1 h	 (76)	7
	Ti powder, TMSCl, DME, reflux, 19 h	 (92)	83
	See table.		7

	Solvent	Temp	Time (h)	
SmI_2	THF	rt	1	(31)
$NbCl_3$(DME)	DME	reflux	21	(77)
$NbCl_5$, Zn	THF	reflux	3	(79)
WCl_4, BuLi	THF	reflux	26	(97)
Mg-graphite	—	reflux	4	(27)
VCl_3, Zn	THF	reflux	20	(55)
$ZrCl_4$, Zn	DME	reflux	1.5	(39)

C_{20-21}

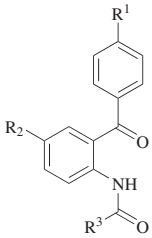


1. $TiCl_3$, C_8K, THF, reflux, 1.5 h
2. Reflux, time 1
3. Reflux, time 2

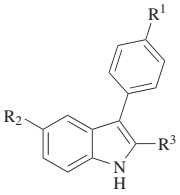
 79

R^1	R^2	Time 1 (h)	Time 2 (h)	
F	H	8	0	(94)
H	Cl	8	0	(86)
Br	H	8	0	(81)
H	I	0	1	(80)
MeO	H	3	0	(86)
H	CF_3	8	0	(83)
H	NC	3	0	(76)

C_{20}

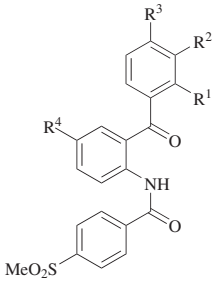
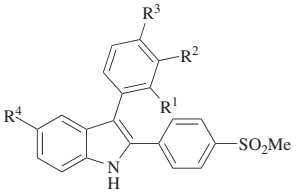


$TiCl_4$, Zn, THF, reflux

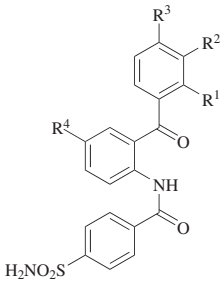
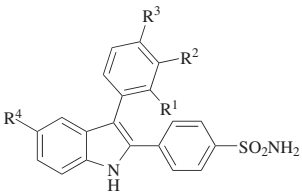


R^1	R^2	R^3		
H	F	4-$H_2NO_2SC_6H_4$	(76.9)	
H	Cl	4-$H_2NO_2SC_6H_4$	(72.3)	
H	Cl	4-$MeO_2SC_6H_4$	(75.4)	763
MeO_2S	Cl	2-FC_6H_4	(78.1)	
MeO_2S	Cl	Ph	(82.4)	
MeO_2S	Cl	4-ClC_6H_4	(77.1)	

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20-22}			
	$TiCl_4$, Zn, THF, reflux, 1.5 h	 (—)	764

R^1	R^2	R^3	R^4
H	H	H	H
H	H	F	H
H	H	Cl	H
H	H	Br	H
H	H	MeO	H
H	H	Me	H
H	Me	Me	H
H	H	Cl	Cl
H	Cl	H	Cl
Cl	H	H	Cl
H	H	H	F
H	H	H	Cl
H	H	H	Br
H	H	H	Me

	$TiCl_4$, Zn, THF, reflux, 1.5 h	 (—)	764

R^1	R^2	R^3	R^4
H	H	H	H
H	H	F	H
H	H	Cl	H
H	H	Br	H
H	H	MeO	H
H	H	Me	H
H	Me	Me	H
H	H	Cl	Cl
H	Cl	H	Cl
Cl	H	H	Cl
H	H	H	F
H	H	H	Cl
H	H	H	Br
H	H	H	Me

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

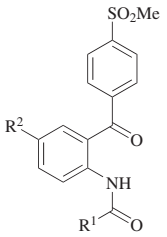
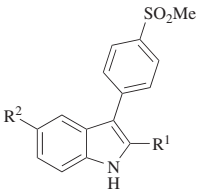
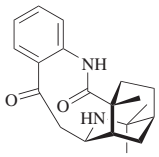
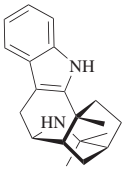
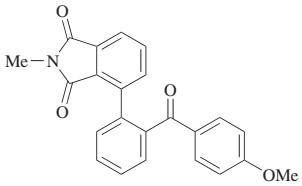
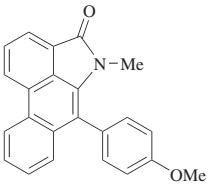
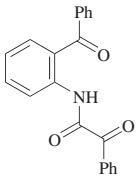
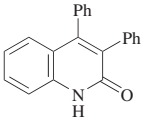
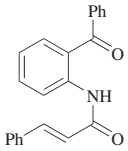
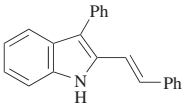
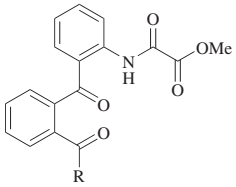
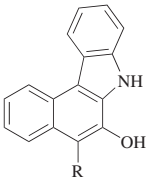
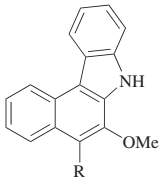
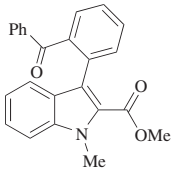
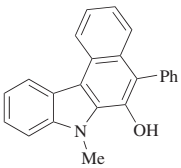
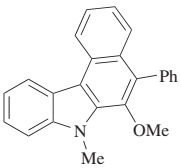
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20-21} 	$TiCl_4$, Zn, THF, reflux, 1.5 h	 (—) R^1 / R^2: Ph / Cl; 2-FC_6H_4 / Cl; 4-ClC_6H_4 / Cl; 4-MeC_6H_4 / Cl; 4-$MeOC_6H_4$ / Cl; 2-$MeO_2CC_6H_4$ / Cl; 4-$MeO_2CC_6H_4$ / Cl; 4-$MeO_2SC_6H_4$ / Cl; 4-$MeO_2SC_6H_4$ / Me	765
C_{20} 	$TiCl_3$, Zn, THF, reflux, 4 h	 (75)[b]	7
C_{21} 	$TiCl_3$, C_8K, DME, reflux	 (86)	137
	1. Ti powder, TMSCl, DME, reflux, 67 h 2. Addition in one lot, reflux 3. Reflux, 2.5 h	 (73)	83
C_{22} 	1. $TiCl_3$, C_8K, THF, reflux, 1.5 h 2. Reflux, 8 h	 (68)	79
 R = 4-$MeOC_6H_4$	$TiCl_3$, C_8K, DME, reflux, 40 min	 **I** +  **II** **I** + **II** (54), **I/II** = 9:1	137
	$TiCl_3$, C_8K, py, DME, reflux	 **I** +  **II** **I** + **II** (89), **I/II** = 5:1	137

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

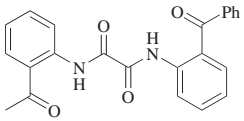
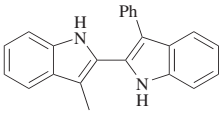
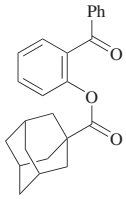
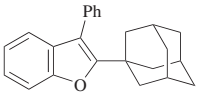
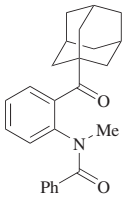
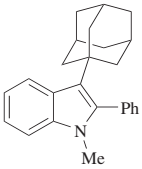
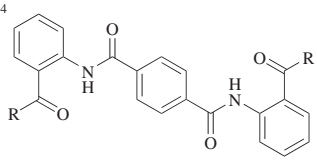
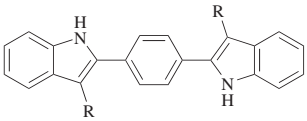
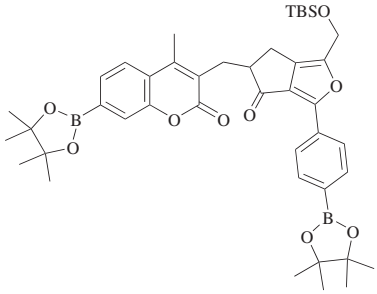
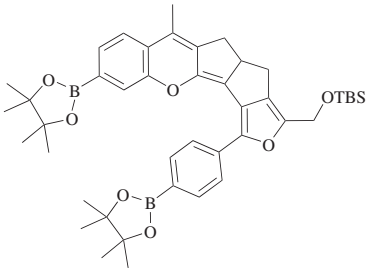
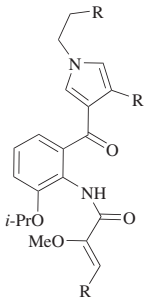
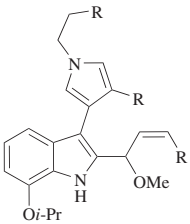
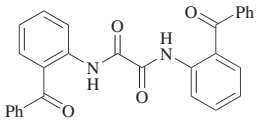
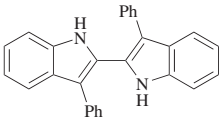
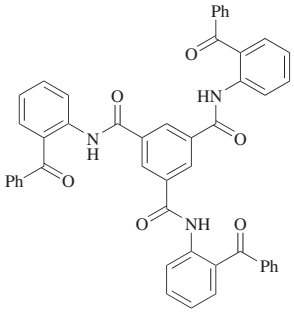
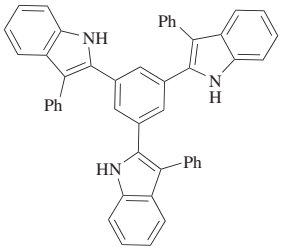
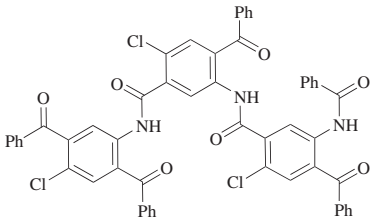
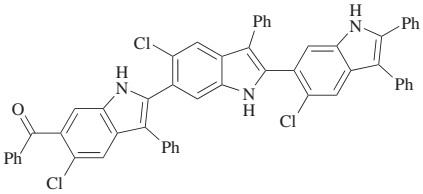
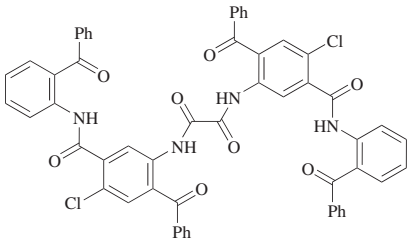
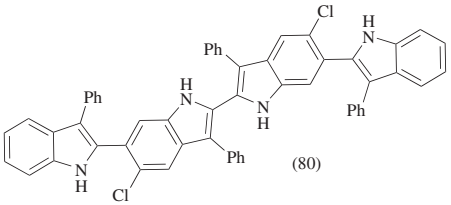
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{23} 	$TiCl_4$, Zn, DME, reflux, 20 h	 (76)	766
C_{24} 	Ti powder, TMSCl, DME, reflux, 16 h	 (91)	83
	$TiCl_3$, Zn, DME, reflux, 1 h	 (79)	755
$C_{24–34}$ 	$TiCl_4$, Zn, DME, reflux	 R Time (h): Me 23 (77); Ph 2 (88)	766
C_{25} 	$TiCl_3$, $LiAlH_4$	 (—)	767
C_{34}  R = 4-$MeOC_6H_4$	1. $TiCl_3$, C_8K, DME, reflux, 1.5 h 2. Py, reflux, 15 min 3. Reflux, 1.5 h	 (71–93)	768, 769

TABLE 3D. INTRAMOLECULAR COUPLING OF OXO ESTERS, OXO AMIDES, AND RELATED COMPOUNDS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{28}			
	$TiCl_3$, M		
	M Solvent Temp Time (h)		
	Zn DME reflux 3	(81)	766, 471
	C_8K THF — 3.5	(65)	766
C_{48}			
	$TiCl_4$, Zn, DME, reflux, 2 h	 (95)	766
C_{55}			
	$TiCl_4$, Zn, DME, reflux, 1.5 h	 (86)	766
C_{56}			
	$TiCl_4$, Zn, DME, reflux, 2.5 h	 (80)	766

[a] The product was isolated after acid hydrolysis.

[b] Optically active starting material was employed.

TABLE 4A. TANDEM HOMOCOUPLING

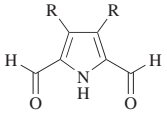
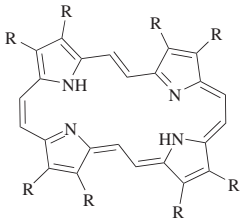
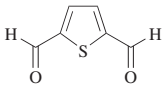
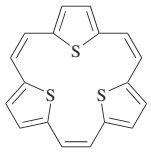
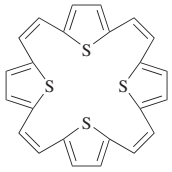
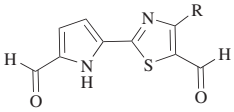
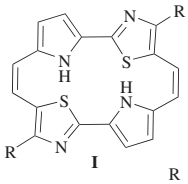
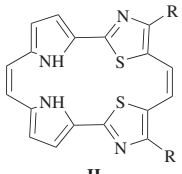
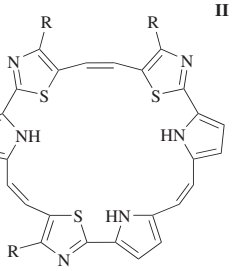
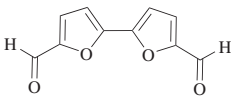
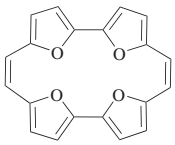
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{6-10}			
	$TiCl_4$, Zn/Cu, THF	 R: H (0.1–0.2); Et (1)	770
C_6			
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Py, reflux 3. Reflux, 18 h	 (38) +  (4.7)	149
C_{9-15}			
	1. $TiCl_4$, Zn/Cu, py, THF, reflux, 2 h 2. Reflux, 60 h 3. Reflux, 5 h	 **I** +  **II**	771
		R: H (7) (0) (0); *t*-Bu (18) (3) (5); Ph (14) (2) (—) +  **III**	
C_{10}			
	$TiCl_4$, Zn	 (16)	772

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

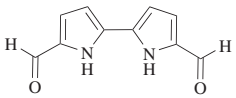
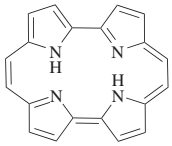
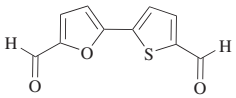
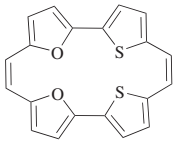
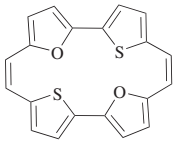
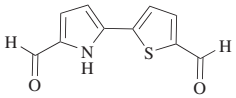
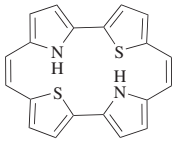
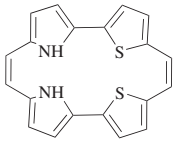
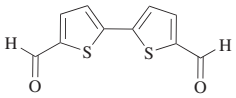
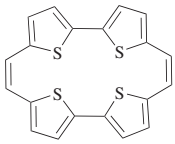
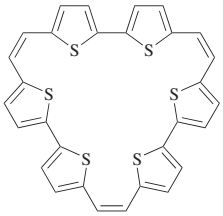
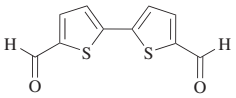
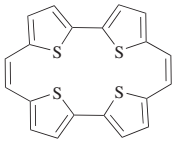
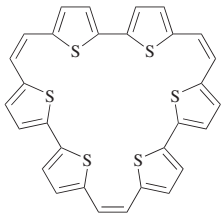
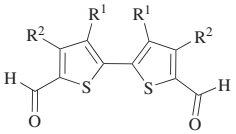
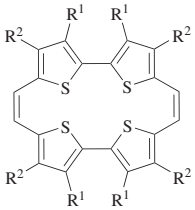
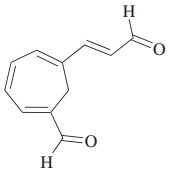
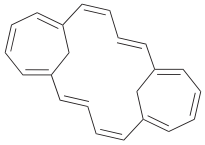
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}			
	1. $TiCl_4$, Zn, py, THF 2. Reflux 3. Reflux, 4 h	 (2–3)[a]	773
	$TiCl_4$, Zn, py, THF, reflux, 2.5 h	 (7.2) +  (2.6)	151
	1. $TiCl_4$, Zn, py, THF 2. Slow addition, reflux 3. Reflux, 1 h	 (8.1) +  (0.4)	774
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Dropwise addition, py, reflux 3. Reflux, 18 h	 (10.5) +  (13.6)	149
	1. $TiCl_4$, Zn/Cu, py, THF 2. Reflux, 13 h 3. Reflux, 1 h	 (8.4) +  (2.9)	775
	1. $TiCl_4$, Zn/Cu, THF, reflux, 2 h 2. Reflux, 42 h 3. Reflux, 30 h	 R^1 R^2 H Br (26); Br H (8.8)	776
C_{11}			
	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Dropwise addition, reflux 3. Reflux, 6 h	 (1.7)	226

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

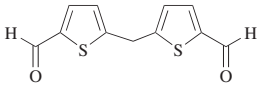
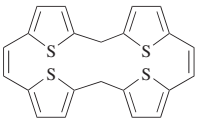
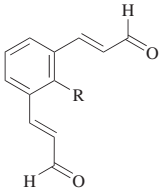
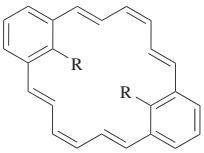
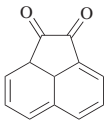
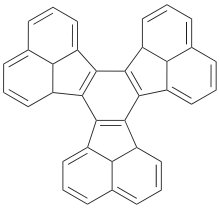
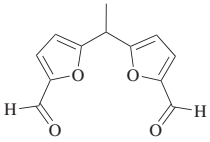
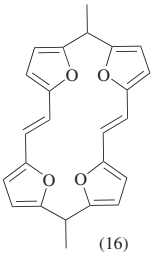
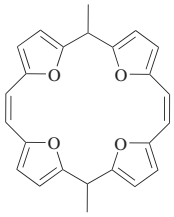
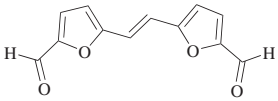
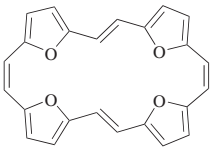
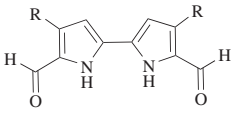
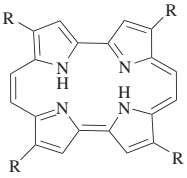
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}			
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Py, reflux, 30 min 3. Reflux, 18 h	 (75)	777, 149
C_{12-13}			
	1. $TiCl_4$, Zn, py, dioxane, reflux, 2.5 h 2. Reflux, 5 h 3. Reflux, 1 h	 R: H (11); Me (18)	778
C_{12}			
	Bis(η^6-biphenyl)Ti(0), toluene, reflux, 2h	 (12–15)	779
	1. $TiCl_4$, Zn/Cu, THF, reflux, 1 h 2. Reflux, 60 h 3. Reflux, 2 h	 (16) +  (10)	780
	$TiCl_4$, Zn/Cu, THF	 (7)	781
C_{12-16}			
	1. $TiCl_4$, Zn, py, THF 2. Reflux 3. Reflux, 30 min	 R: Me (2); Et (4); Pr (10)	782

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

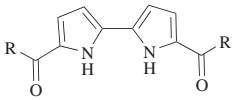
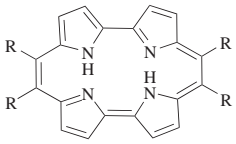
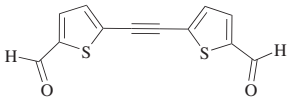
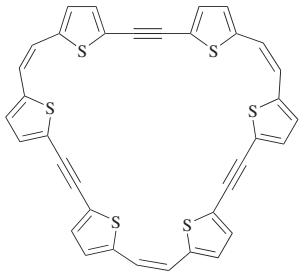
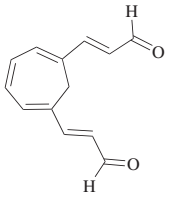
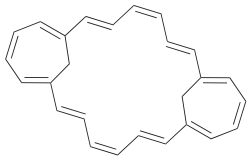
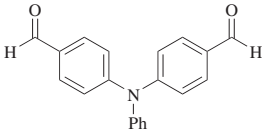
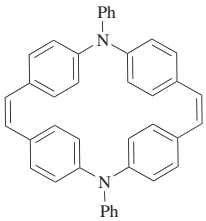
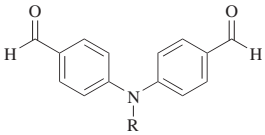
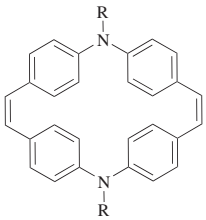
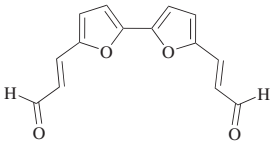
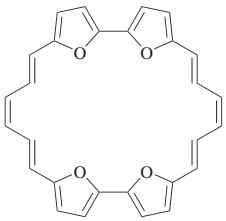
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-16}			
	1. $TiCl_4$, Zn, py, THF 2. Addition in one lot 3. Reflux, 3 h	 R: Me (2.5); Et (5); Pr (7)	783
C_{12}			
	1. $TiCl_3(DME)_{1.5}$, Zn/Cu, DME 2. rt, 12 h 3. Reflux, 6 h	 (10–15)	784
C_{13}			
	1. $TiCl_3$, $LiAlH_4$, DME, reflux, 30 min 2. Reflux, 6 h 3. Reflux, 6 h	 (4.8)	226
C_{14}			
	1. $TiCl_4$, Zn, CH_2Cl_2, reflux, 1 h 2. Dropwise addition, py, reflux 3. Reflux, 8 h	 (9)	785
 R = 4-BuC_6H_4	$TiCl_4$, Zn, py, THF, reflux, 8 h	 (6.7)	786
	1. $TiCl_4$, Zn/Cu, py, THF, reflux, 1 h 2. Reflux, 24 h 3. Reflux, 6 h	 (13)	787

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

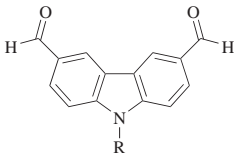
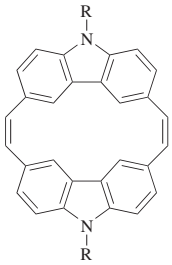
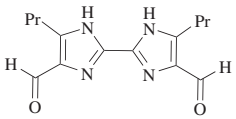
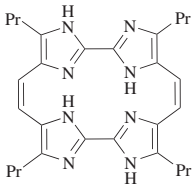
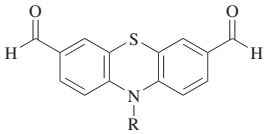
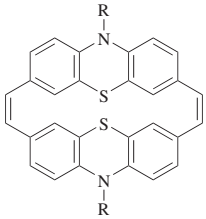
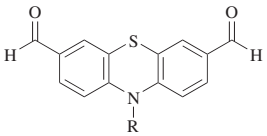
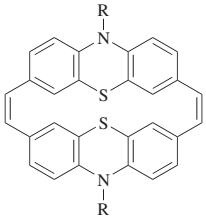
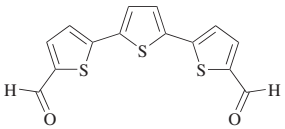
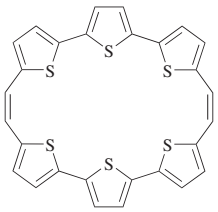
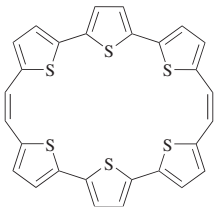
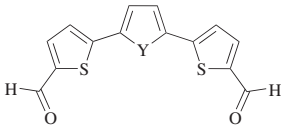
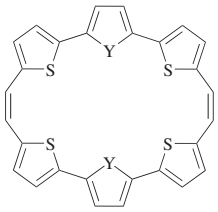
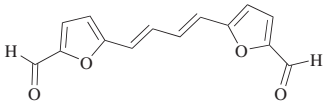
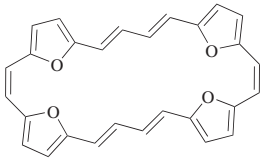
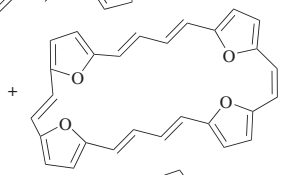
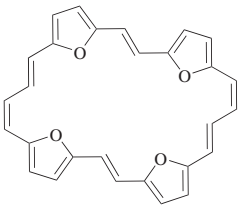
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Dropwise addition, py, reflux 3. Reflux, 10 h	 R: Bu (8.1); Ph (5.6)	377
	1. $TiCl_4$, Zn, py, THF, reflux, 3 h 2. Addition in one lot, reflux 3. Reflux, 4 h	 (2)	788
	$TiCl_4$, Zn	 R: dioxane, heat, 2–3 d (84) R: dioxane, heat, 2–3 d (49)	789 789
		 R: n-C_6H_{13}, — , dioxane, heat, 2–3 d (78) R: Bn, — , dioxane, heat, 2–3 d (54) R: n-C_7H_{15}, py, THF, reflux, 12 h (26)	789 789 790
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Py, reflux 3. Reflux, 18 h	 (64)	149
	$TiCl_3$, $LiAlH_4$, THF, reflux, 12 h	 (1)	775

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}			
	$TiCl_4$, Zn, py, THF	 Y: S (64); MeN (>69); n-$C_{12}H_{25}N$ (>69)	791
	1. $TiCl_4$, Zn/Cu, THF, reflux, 3 h 2. Reflux, 36 h 3. Reflux, 4 h	 (—) +  (—) +  (—)	792

C_{15}

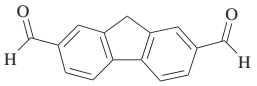
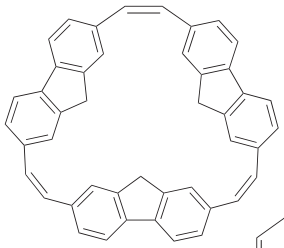
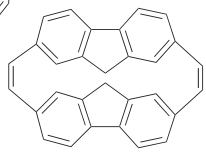
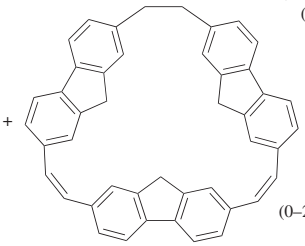
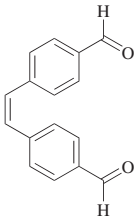
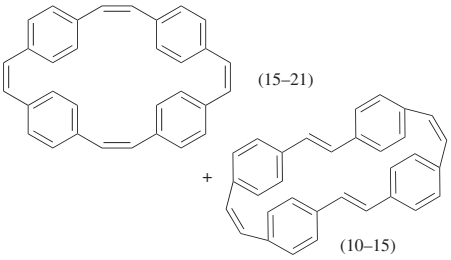
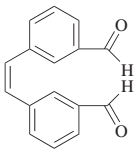
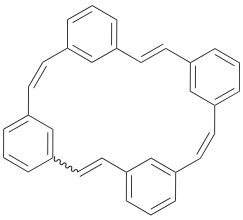
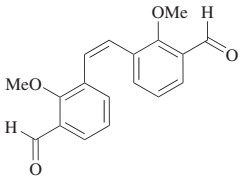
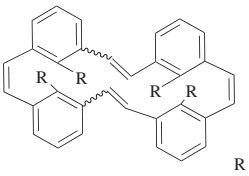
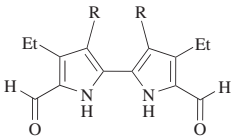
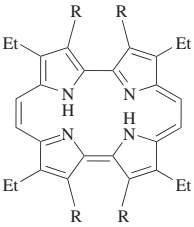
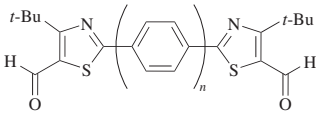
	1. $TiCl_4$, Zn, CuI, DME, reflux, 4 h 2. 0°, 2 h 3. rt, overnight; then reflux, 6 h	 (8–13) +  (3–5) +  (0–2)	793

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

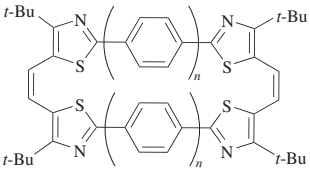
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}			
	1. $TiCl_3(DME)_{1.5}$ or $TiCl_4$, Zn/Cu, DME 2. rt, 1 h 3. Reflux, 4–6 h	 (15–21) + (10–15)	794
	$TiCl_4$, Zn, DME	 (20–50)	795
	$TiCl_4$, Zn, THF	 (26) R = MeO	796
C_{16-18}			
	1. $TiCl_4$, Zn, CuCl, THF, reflux, time 1 2. Reflux, 15 min 3. Reflux, time 2		

R	Time 1 (h)	Time 2 (min)		Refs.
Me	2	2	(16)	797, 798
Et	3	3	(15)	798

C_{16-22}



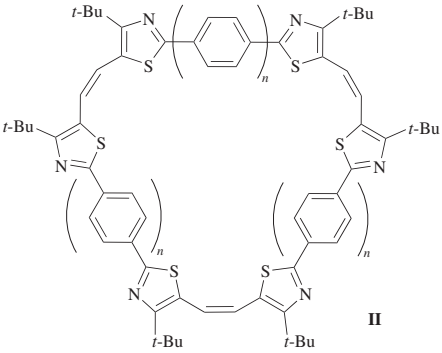
1. $TiCl_4$, Zn/Cu, py, THF, reflux, 2 h
2. Reflux, 60 h
3. Reflux, 5 h



I

n	**I**	**II**	Refs.
0	(6.4)	(9.8)	799
1	(9.8)	(21.8)	

+



II

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

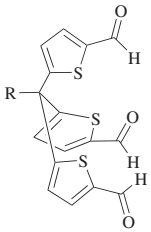
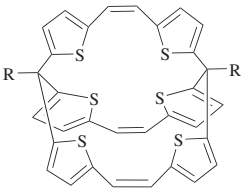
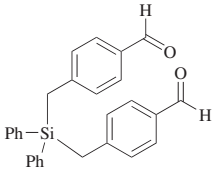
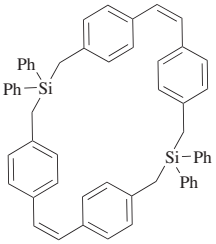
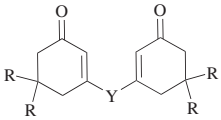
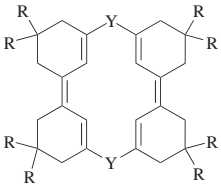
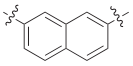
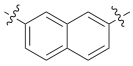
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{16–22}$ 	$TiCl_4$, Zn/CuI, DME, rt, overnight; then reflux, 24 h	 R: H (2–4)	800
		Me (8)	801
		n-C_6H_{13} (7)	801
C_{16} 	1. $TiCl_4$, Zn, DME, reflux, 1 h 2. Dropwise addition, rt 3. Reflux, 20 h	 (1.1)	356
$C_{18–26}$ 	$TiCl_4$, Zn, dioxane		448
		Y: R: H (36)	
		Y: R: Me (20)	
		Y:  R: H (20)	
		Y:  R: Me (4)	

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

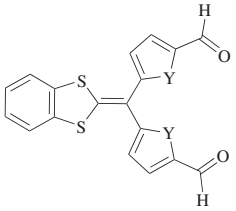
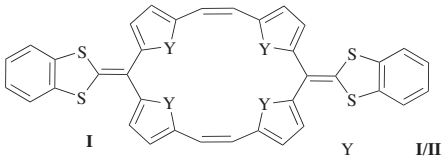
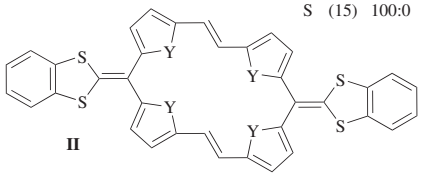
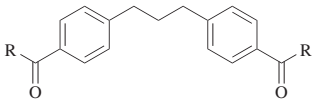
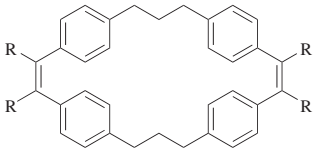
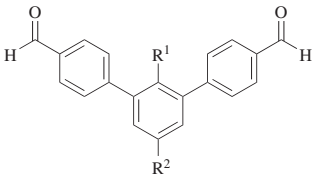
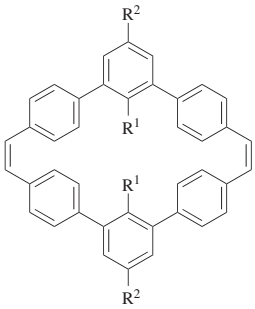
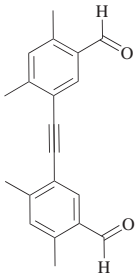
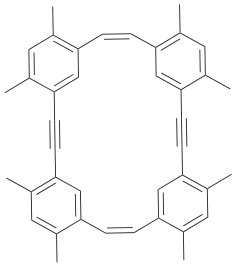
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}			
	1. $TiCl_4$, Zn/Cu, THF, reflux, 2 h 2. Reflux, 48 h 3. Reflux, 1 h	 **I** Y — I/II O (15) — 10:4 S (15) — 100:0 +  **II**	802
$C_{19–21}$			
	1. $TiCl_4$, Zn, py, THF, reflux, 2 h 2. Reflux, 10–12 h	 R — Me (32), Et (58)	234
$C_{20–21}$			
	1. $TiCl_4$, Zn, py, THF, reflux, 1 h 2. Addition in one lot, reflux 3. Reflux, 6 h	 R^1 — R^2 H — H (24) Br — H (18) H — Br (24) MeO_2C — H (25)	648, 647
C_{20}			
	1. $TiCl_4$, Zn, CuI, DME, reflux, 3 h 2. rt, 7 h 3. rt, 15 h	 (11)	232

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

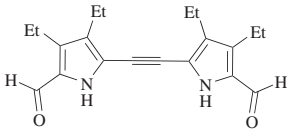
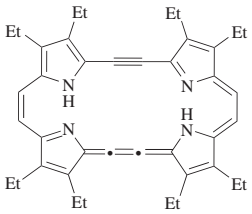
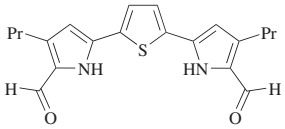
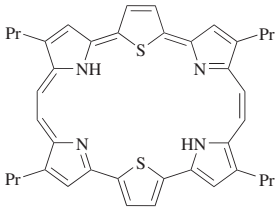
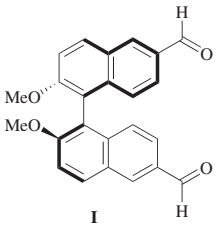
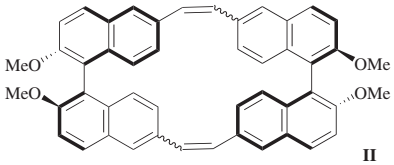
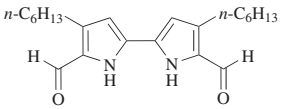
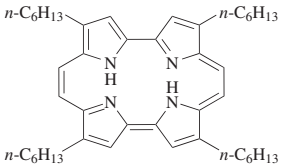
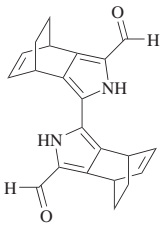
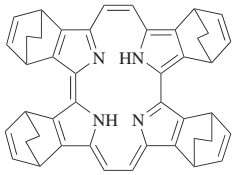
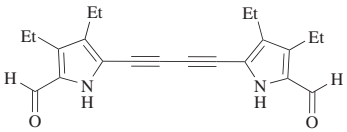
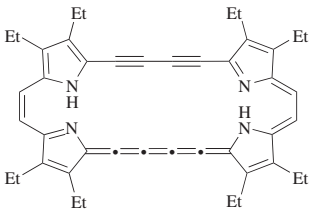
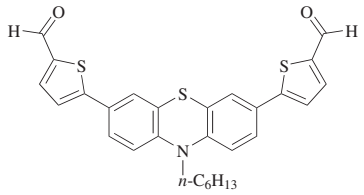
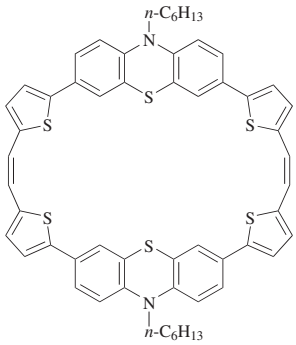
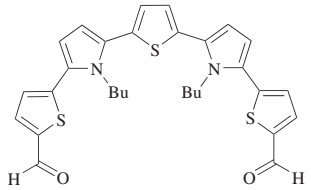
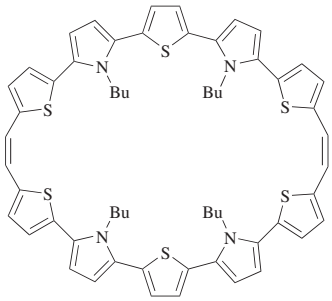
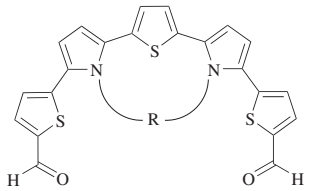
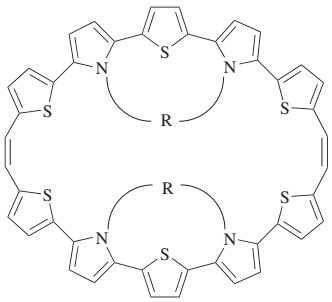
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}			
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 3 h 2. Addition in small portions, reflux 3. Reflux, 10 min	 (18)	803
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Py, reflux, 1.5 h 3. Reflux, 16 h 4. Air oxidation, $CHCl_3$, 1 h	 (28)	804
C_{22}			
 **I**	1. $TiCl_4$, Zn, CuI, DME, reflux, 3.5 h 2. rt, 30 min 3. rt, 17 h; then reflux, 6 h	 **II** **I** racemic (*R*) (*S*) **II** racemic (*R*,*R*) (*S*,*S*) racemic (16) (~40) (46)	805
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 2 h 2. Reflux, 2 h 3. Reflux, 1 h	 (21)	152
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 2 h 2. Reflux, 1 h 3. Reflux, 1 h	 (24)	152
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 3 h 2. Reflux 3. Reflux, 10 min	 (9)	806

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{22}			
	$TiCl_4$, Zn, dioxane, heat, 2–3 d	 (81)	789
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Reflux 3. Reflux, 40 h	 (34)	662
	1. $TiCl_4$, Zn, THF/CH_2Cl_2, reflux, 1 h 2. Reflux 3. Reflux, 40 h		662

R	
$(CH_2)_8$	(14)
$(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3$	(37)

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

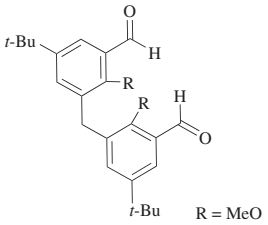
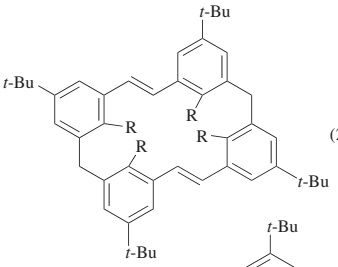
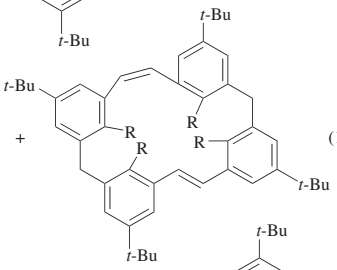
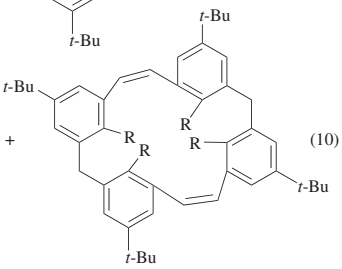
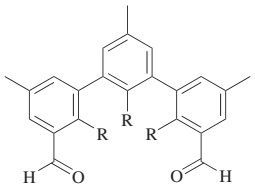
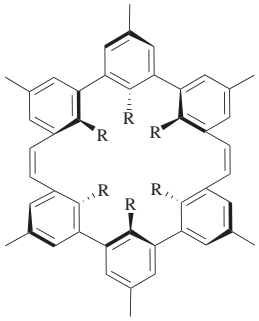
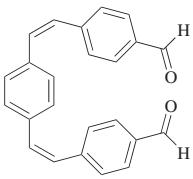
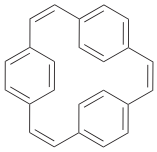
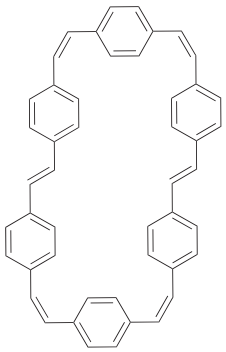
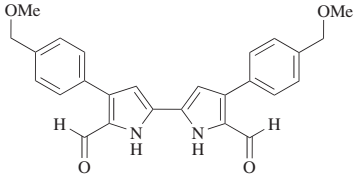
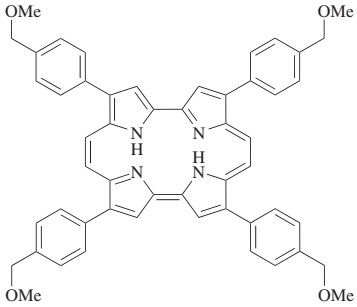
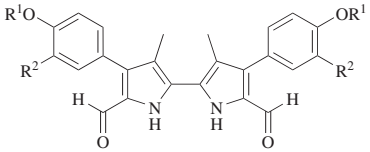
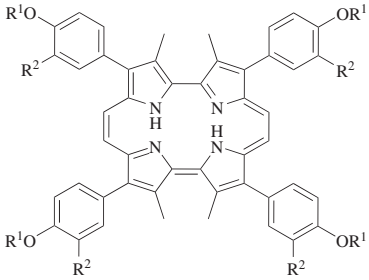
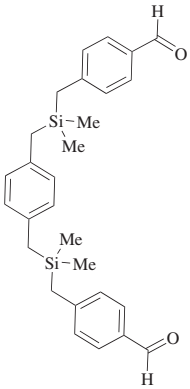
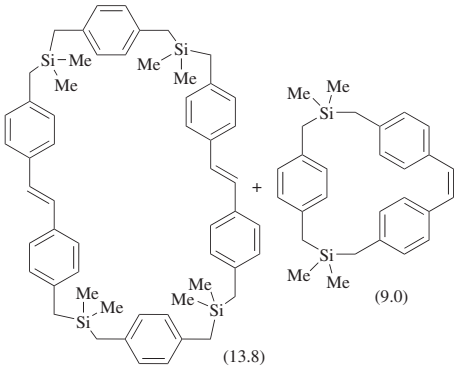
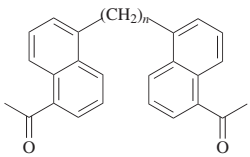
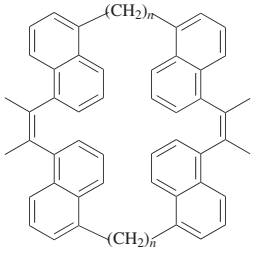
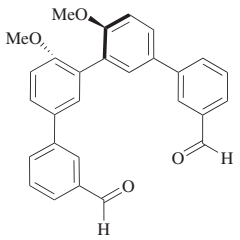
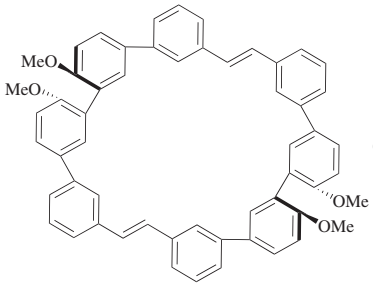
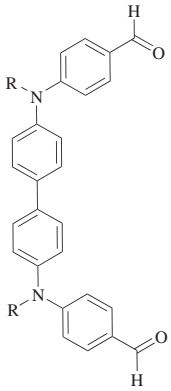
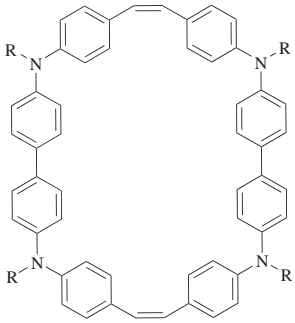
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{23}			
	1. $TiCl_4$, Zn, THF, 55°, 2 h 2. Dropwise addition, 55° 3. 55°, 48 h	 (24)  (1)  (10)	807
	1. $TiCl_4$, Zn, KBr, dioxane, reflux, 2 h 2. Reflux, 48 h 3. Reflux, 48 h	 (14.4)	808
C_{24}			
	1. $TiCl_4$, Zn, solvent, reflux, 2 h 2. rt, 30 min 3. rt, 12 h; then reflux, 5 h	 **I** +  **II** Solvent: DME — **I** (34), **II** (12)[b]; DME/toluene (1:1) — **I** (3), **II** (53)	314

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

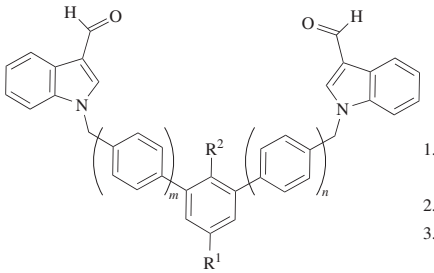
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}			
	$TiCl_4$, Zn, CuCl; then O_2	 (—)	809
$C_{24–44}$			
	1. $TiCl_4$, Zn, CuCl, THF, reflux, 3 h 2. Reflux, 0.5–1 h 3. Reflux, 12 h	 R^1 / R^2: n-$C_{10}H_{21}$ / H (41); n-$C_{10}H_{21}$ / n-$C_{10}H_{21}O$ (33)	810

C_{24}			
	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Dropwise addition, rt 3. Reflux, 24 h	 (13.8) + (9.0)	356
$C_{25–26}$			
	1. $TiCl_4$, Zn/Cu, DME, reflux, 2 h 2. Reflux, 72 h 3. Reflux, 12 h	 n: 1 (64); 2 (40)	150

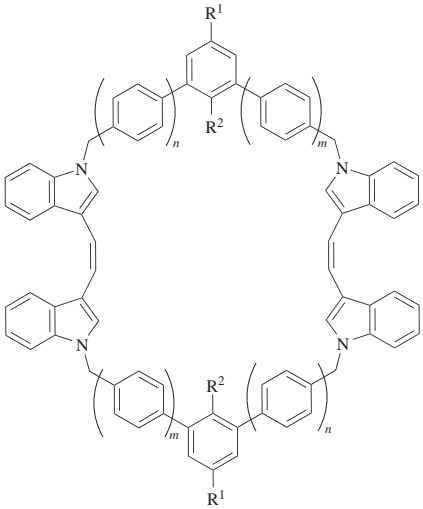
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{26}			
	1. $TiCl_4$, Zn, CuI, DME/toluene, reflux, 3 h 2. rt, 30 min 3. rt, overnight; then reflux, 8 h	 (37)	811
 R = 4-BuC_6H_4	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Dropwise addition, py, reflux 3. Reflux, 8 h	 (22.1)	786

442

$C_{26–38}$



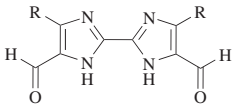
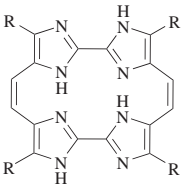
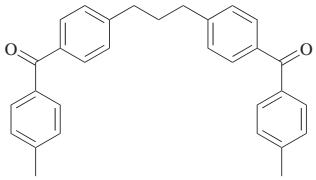
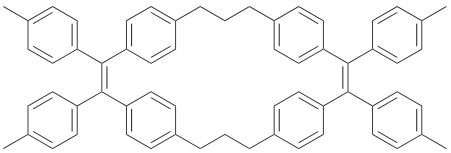
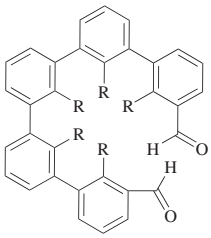
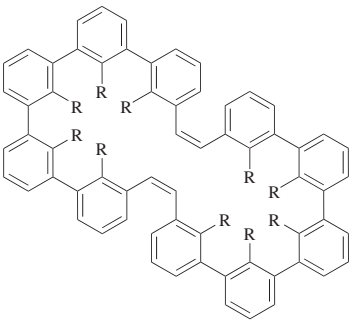
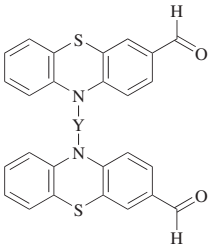
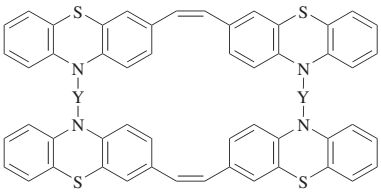
1. $TiCl_4$, Zn, py, THF, reflux, 1 h
2. Addition in one lot, reflux
3. Reflux, overnight



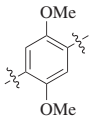
m	*n*	R^1	R^2		Refs.
0	0	H	H	(20)	648, 647
0	0	MeO	MeO	(23)	648, 647
1	0	H	H	(18)	648, 647
1	1	H	H	(8)	647
1	1	H	Br	(6)	647
1	1	H	I	(5)	647
1	1	Br	H	(8)	647

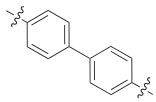
443

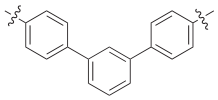
TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{28}  R = 4-BuC_6H_4	1. $TiCl_4$, Zn/Cu, py, THF, reflux, 2 h 2. Dropwise addition, reflux 2. Reflux, 1 h	 (7)	812
C_{31} 	1. $TiCl_4$, Zn, dioxane, reflux, 2 h 2. Reflux, 80 h 3. Reflux, 10 h	 (6.6)	234
C_{32}  R = MeO	1. $TiCl_3$, Zn/Cu, DME, reflux, 1 h 2. Reflux, 6 d 3. Reflux, 2 d	 (5.2)	813
C_{32-44} 	$TiCl_4$, Zn, py, THF, reflux, overnight		790

Y

 (28)

 (25)

 (19)

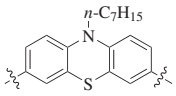
 (19)

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

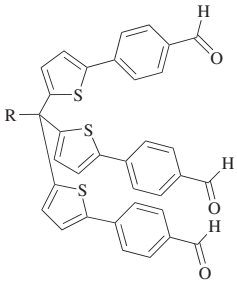
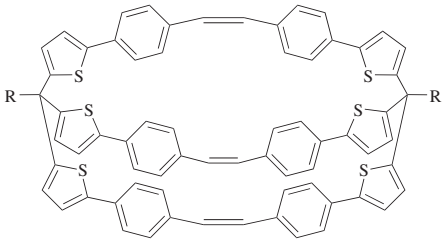
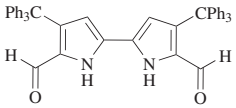
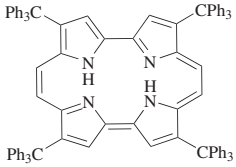
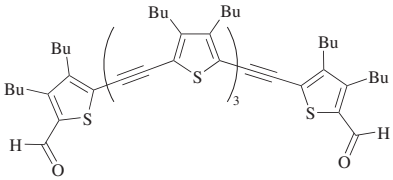
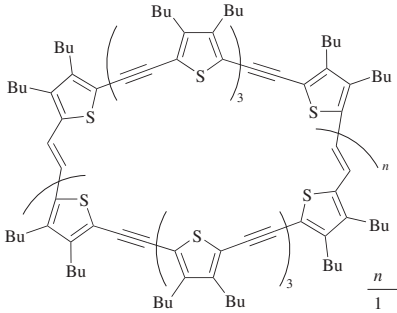
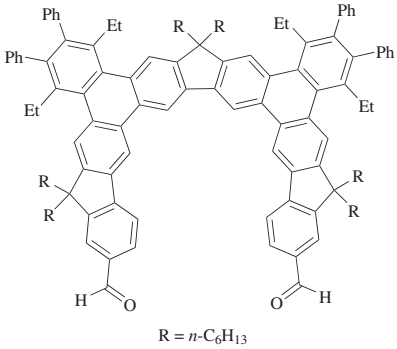
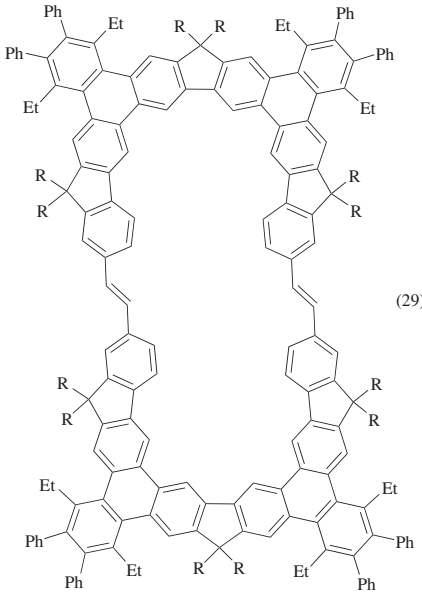
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{35–40}$ 	$TiCl_4$, Zn/CuI, DME, reflux	 R: Me (17); *n*-C_6H_{13} (16)	814
C_{48} 	$TiCl_4$, Zn	 (3)	815
C_{70} 	1. $TiCl_4$, Zn, THF, reflux, 3 h 2. Py, reflux, 2 h 3. Reflux, 18 h	 *n*: 1 (32); 2 (9); 3 (6); 4 (4); 5 (2)	816

TABLE 4A. TANDEM HOMOCOUPLING (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{121}			
 R = *n*-C_6H_{13}	1. $TiCl_4$, Zn, THF, reflux, 1 h 2. Dropwise addition, py, reflux 3. Reflux, 24 h	 (29)	817

[a] The initially formed coupling product was further oxidized to porphycene.

[b] The product is a mixture of stereoisomers.

TABLE 4B. TANDEM MIXED-COUPLING

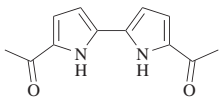
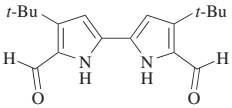
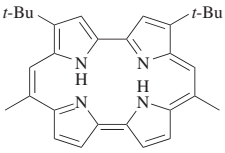
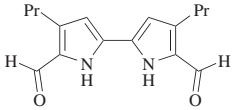
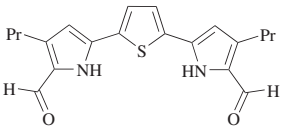
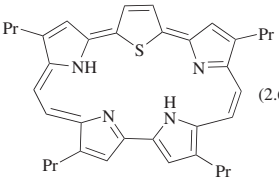
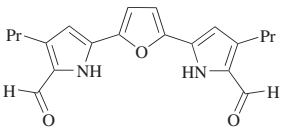
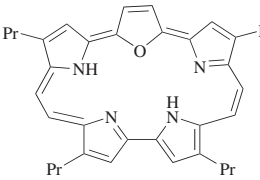
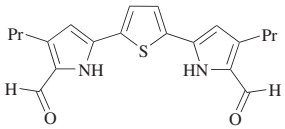
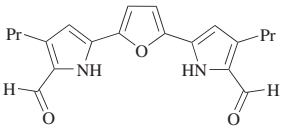
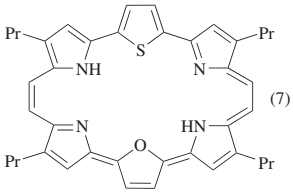
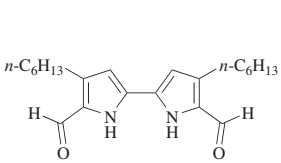
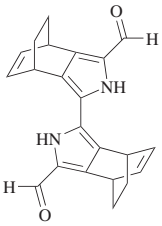
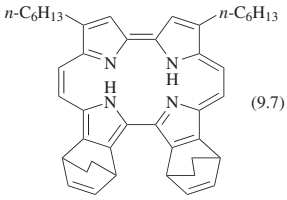
Dicarbonyl 1	Dicarbonyl 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}				
		$TiCl_4$, Zn	 (7)	815
C_{16}				
		1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Py, reflux, 20 min 3. Reflux, 20 h	 (2.6)	818
		1. $TiCl_4$, Zn, reflux, 15 h 2. Py, reflux, 4 h 3. Reflux, 17 h	 (5)	819

TABLE 4B. TANDEM MIXED-COUPLING (*Continued*)

Dicarbonyl 1	Dicarbonyl 2	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{20}				
		1. $TiCl_4$, Zn, THF, reflux, 30 min 2. Py, reflux, 1.5 h 3. Reflux, 16 h	 (7)	818
C_{22}				
		1. $TiCl_4$, Zn, CuCl, THF, reflux, 2 h 2. Reflux, 2 h 3. Reflux, 1 h	 (9.7)	152

REFERENCES

[1] Schreibmann, A. A. P. *Tetrahedron Lett.* **1970**, 4271.
[2] Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.
[3] Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.
[4] Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147.
[5] McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708.
[6] McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748.
[7] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
[8] Armbruster, J.; Grabowski, S.; Ruch, T.; Prinzbach, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2242.
[9] Auderset, P. C.; Gartenmann, T. C. C.; Gesing, E. R. F. *Kontakte (Darmstadt)* **1985**, *3*, 14.
[10] Betschart, C.; Seebach, D. *Chimia* **1989**, *43*, 39.
[11] Dang, Y.; Geise, H. J. *Janssen Chim. Acta* **1988**, *6*, 3.
[12] Dang, Y.; Geise, H. J. *Janssen Chim. Acta* **1989**, *7*, 3.
[13] Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Edward, W. A., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: Oxford, 1995; Vol. 12 pp 1071–1095.
[14] Ephritikhine, M.; Villiers, C. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley–VCH: Weinheim, 2004, pp 223–285.
[15] Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442.
[16] Fürstner, A. In *Transition Metals for Organic Synthesis (2nd Edition)*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004, pp 449–468.
[17] Kahn, B. E.; Rieke, R. D. *Organometallics* **1988**, *7*, 463.
[18] König, B. *J. Prak. Chem./Chem.-Ztg.* **1995**, *337*, 250.
[19] Ladipo, F. T. *Curr. Org. Chem.* **2006**, *10*, 965.
[20] Lectka, T. *Active Metals* **1996**, 85.
[21] Lenoir, D. *Synthesis* **1989**, 883.
[22] McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405.
[23] McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.
[24] Takeda, T.; Tsubouchi, A. In *Science of Synthesis*; Rawal, V. H.; Kozmin, S. A., Eds.; Thime: Stuttgart, 2009; Vol. 46, pp 63–96.
[25] Welzel, P. *Nachr. Chem. Tech. Lab.* **1983**, *31*, 814.
[26] Ephritikhine, M. *Chem. Commun.* **1998**, 2549.
[27] McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.
[28] Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *50*, 145.
[29] Ozerov, O. V.; Brock, C. P.; Carr, S. D.; Ladipo, F. T. *Organometallics* **2000**, *19*, 5016.
[30] Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. Y. *J. Org. Chem.* **1982**, *47*, 248.
[31] Pierce, K. G.; Barteau, M. A. *J. Org. Chem.* **1995**, *60*, 2405.
[32] Aleandri, L. E.; Becke, S.; Bogdanović, B.; Jones, D. J.; Rozière, J. *J. Organomet. Chem.* **1994**, *472*, 97.
[33] Bogdanović, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109.
[34] Eisch, J. J.; Shi, X.; Lasota, J. *Z. Naturforsch. B* **1995**, *50*, 342.
[35] Stahl, M.; Pidun, U.; Frenking, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2234.
[36] Covert, K. J.; Wolczanski, P. T.; Hill, S. A.; Krusic, P. J. *Inorg. Chem.* **1992**, *31*, 66.
[37] Villiers, C.; Ephritikhine, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2380.
[38] Villiers, C.; Ephritikhine, M. *Chem.-Eur. J.* **2001**, *7*, 3043.
[39] Villiers, C.; Vandais, A.; Ephritikhine, M. *J. Organomet. Chem.* **2001**, *617-618*, 744.
[40] Villiers, C.; Adam, R.; Lance, M.; Nierlich, M.; Vigner, J.; Ephritikhine, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1144.
[41] Ephritikhine, M.; Maury, O.; Villiers, C.; Lance, M.; Nierlich, M. *J. Chem. Soc., Dalton Trans.* **1998**, 3021.
[42] Maury, O.; Villiers, C.; Ephritikhine, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1129.
[43] Paquette, L. A.; Wells, G. J.; Wickham, G. *J. Org. Chem.* **1984**, *49*, 3618.
[44] Gupta, S.; Kar, G. K.; Ray, J. K. *Synth. Commun.* **2000**, *30*, 2393.
[45] Fujiwara, Y.; Ishikawa, R.; Akiyama, F.; Teranishi, S. *J. Org. Chem.* **1978**, *43*, 2477.

[46] Bhilare, S. V.; Darvatkar, N. B.; Deorukhkar, A. R.; Rasalkar, M. S.; Salunkhe, M. M. *Synth. Commun.* **2007**, *37*, 3111.
[47] Lenoir, D.; Burghard, H. *J. Chem. Res. (S)* **1980**, 396.
[48] Leimner, J.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 3697.
[49] Senge, M. O.; Gerzevske, K. R.; Vicente, M. G. H.; Forsyth, T. P.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 750.
[50] Kalisch, W. W.; Senge, M. O.; Ruhlandt-Senge, K. *Photochem. Photobiol.* **1998**, *67*, 312.
[51] Ace, K. W.; Armitage, M. A.; Bellingham, R. K.; Blackler, P. D.; Ennis, D. S.; Hussain, N.; Lathbury, D. C.; Morgan, D. O.; O'Connor, N.; Oakes, G. H.; Passey, S. C.; Powling, L. C. *Org. Process Res. Dev.* **2001**, *5*, 479.
[52] Chu, G.-H.; Peters, A.; Selcer, K. W.; Li, P.-K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 141.
[53] Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608.
[54] Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* **1985**, *28*, 1504.
[55] Zolotareva, V. A.; Klimova, L. I.; Malanina, G. G.; Sokolova, A. S.; Grinenko, G. S. *Pharm. Chem. J.* **1990**, *24*, 241.
[56] Gauthier, S.; Sancéau, J.–Y.; Mailhot, J.; Caron, B.; Cloutier, J. *Tetrahedron* **2000**, *56*, 703.
[57] Moreau, A.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem.* **2006**, *14*, 5340.
[58] Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Synlett* **2004**, 1513.
[59] Uddin, M. J.; Rao, P. N. P.; McDonald, R.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 6108.
[60] Kahn, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733.
[61] McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655.
[62] McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896.
[63] McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660.
[64] Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178.
[65] Dams, R.; Malinowski, M.; Geise, H. J. *Bull. Soc. Chim. Belg.* **1981**, *90*, 1141.
[66] Mundy, B. P.; Srinivasa, R.; Kim, Y.; Dolph, T.; Warnet, R. J. *J. Org. Chem.* **1982**, *47*, 1657.
[67] Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990.
[68] Eisch, J. J.; Gitua, J. N.; Otieno, P. O.; Shi, X. *J. Organomet. Chem.* **2001**, *624*, 229.
[69] Fürstner, A.; Seidel, G. *Synthesis* **1995**, 63.
[70] Fürstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krüeger, C.; Mynott, R. *Tetrahedron* **1995**, *51*, 8875.
[71] Braga, D.; Ripamonti, A.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 927.
[72] Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1985**, *280*, 307.
[73] Fürstner, A.; Weidmann, H. *Synthesis* **1987**, 1071.
[74] Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729.
[75] Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914.
[76] Burger, P.; Brintzinger, H. H. *J. Organomet. Chem.* **1991**, *407*, 207.
[77] Pitter, S.; Huttner, G.; Walter, O.; Zsolnai, L. *J. Organomet. Chem.* **1993**, *454*, 183.
[78] Fürstner, A.; Jumbam, D. N.; Weidmann, H. *Tetrahedron Lett.* **1991**, *32*, 6695.
[79] Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991.
[80] Fürstner, A.; Jumbam, D. N. *J. Chem. Soc., Chem. Commun.* **1993**, 211.
[81] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
[82] Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127*, 1125.
[83] Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.
[84] Clive, D. L. J.; Zhang, C. Z.; Murthy, K. S. K.; Hayward, W. D.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 6447.
[85] Fürstner, A.; Seidel, G.; Kopiske, C.; Krüeger, C.; Mynott, R. *Liebigs Ann.* **1996**, 655.
[86] Chen, T. L.; Chan, T. H.; Shaver, A. *J. Organomet. Chem.* **1984**, *268*, C1.
[87] Okamoto, S.; He, J.-Q.; Ohno, C.; Oh-iwa, Y.; Kawaguchi, Y. *Tetrahedron Lett.* **2010**, *51*, 387.
[88] Dutta, D. K.; Konwar, D. *Tetrahedron Lett.* **2000**, *41*, 6227.
[89] Sato, R.; Nagaoka, T.; Saito, M. *Tetrahedron Lett.* **1990**, *31*, 4165.

[90] Schmidt, A.; Beckert, R.; Weiß, D. *Tetrahedron Lett.* **1992**, *33*, 4299.
[91] Banerjee, A. K.; de Carrasco, M. C. S.; Frydrychhouge, C. S. V.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1803.
[92] Denifl, P.; Hradsky, A.; Bildstein, B.; Wurst, K. *J. Organomet. Chem.* **1996**, *523*, 79.
[93] Lee, S. J.; Kim, T. Y.; Choi, K. S.; Park, M. K.; Han, B. H. *Bull. Korean Chem. Soc.* **1997**, *18*, 224.
[94] Eisch, J. J.; Fregene, P. O. *Eur. J. Org. Chem.* **2008**, 4482.
[95] Sato, M.; Oshima, K. *Chem. Lett.* **1982**, 157.
[96] Kauffmann, T.; Kallweit, H. *Chem. Ber.* **1992**, *125*, 149.
[97] Szymoniak, J.; Luque, L.; Besançon, J.; Moïse, C. *Bull. Soc. Chim. Fr.* **1994**, *131*, 89.
[98] Howarth, J.; Finnegan, J. *Synth. Commun.* **1997**, *27*, 3663.
[99] Chisholm, M. H.; Klang, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 2324.
[100] Chisholm, M. H. *Pure Appl. Chem.* **1991**, *63*, 665.
[101] Chisholm, M. H.; Folting, K.; Klang, J. A. *Organometallics* **1990**, *9*, 602.
[102] Chisholm, M. H.; Folting, K.; Klang, J. A. *Organometallics* **1990**, *9*, 607.
[103] Petit, M.; Mortreux, A.; Petit, F. *J. Chem. Soc., Chem. Commun.* **1984**, 341.
[104] Barman, D. C.; Thakur, A. J.; Prajapati, D.; Sandhu, J. S. *Synlett* **2001**, 515.
[105] Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729.
[106] Xu, X.; Zhang, Y. *Tetrahedron* **2002**, *58*, 503.
[107] Xu, X.-L.; Zhang, Y.-M. *Chin. J. Chem.* **2002**, *20*, 1463.
[108] Ogawa, A.; Nanke, T.; Takami, N.; Sekiguchi, M.; Kambe, N.; Sonoda, N. *Appl. Organomet. Chem.* **1995**, *9*, 461.
[109] Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445.
[110] Ishida, A.; Mukaiyama, T. *Chem. Lett.* **1976**, 1127.
[111] Lenoir, D. *Synthesis* **1977**, 553.
[112] Härter, P.; Latzel, K.; Spiegler, M.; Herdtweck, E. *Polyhedron* **1998**, *17*, 1141.
[113] Rele, S.; Chattopadhyay, S.; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093.
[114] Rele, S. M.; Nayak, S. K.; Chattopadhyay, S. *Tetrahedron* **2008**, *64*, 7225.
[115] Talukdar, S.; Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 4925.
[116] McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.
[117] McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249.
[118] Walborsky, H. M.; Wüst, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807.
[119] Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.
[120] Dams, R.; Malinowski, M.; Geise, H. J. *Recl. Trav. Chim. Pays–Bas* **1982**, *101*, 112.
[121] Ramana, M. M. V.; Singh, B. K. D.; Parihar, J. A. *J. Chem. Res.* **2004**, 760.
[122] Hoischen, D.; Colmenares, L. U.; Koukhareva, I.; Ho, M.; Liu, R. S. H. *J. Fluorine Chem.* **1999**, *97*, 165.
[123] Bauchat, P.; Le Bras, N.; Rigal, L.; Foucaud, A. *Tetrahedron* **1994**, *50*, 7815.
[124] Castedo, L.; Cid, M. M.; Domínguez, R.; Seijas, J. A.; Villaverde, M. C. *Heterocycles* **1990**, *31*, 1271.
[125] Kriste, A. G.; Tercel, M.; Anderson, R. F.; Ferry, D. M.; Wilson, W. R. *Radiat. Res.* **2002**, *158*, 753.
[126] Niemi, T.-A.; Coe, P. L.; Till, S. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1519.
[127] Fujita, T.; Kuwahara, S.; Harada, N. *Eur. J. Org. Chem.* **2005**, 4533.
[128] Reddy, S. M.; Duraisamy, M.; Walborsky, H. M. *J. Org. Chem.* **1986**, *51*, 2361.
[129] Pons, J.; Santelli, M. *J. Org. Chem.* **1989**, *54*, 877.
[130] Kühn, R.; Otto, H.-H. *Arch. Pharm.* **1989**, *322*, 375.
[131] Fürstner, A.; Seidel, G.; Mons, H.-E.; Mynott, R. *Eur. J. Inorg. Chem.* **1998**, 1771.
[132] Nagafuji, A.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Kidorui* **1994**, *24*, 198.
[133] Jeong, H. J.; Yoon, U. Y.; Jang, S. H.; Yoo, U.-A.; Kim, S. N.; Truong, B. T.; Shin, S. C.; Yoon, Y.–J.; Singh, O. M.; Lee, S.-G. *Synlett* **2007**, 1407.
[134] Shi, D.-q.; Chen, J.-x.; Chai, W.-y.; Chen, W.-x.; Kao, T.-y. *Tetrahedron Lett.* **1993**, *34*, 2963.

[135] Watanabe, N.; Suganuma, H.; Kobayashi, H.; Mutoh, H.; Katao, Y.; Matsumoto, M. *Tetrahedron* **1999**, *55*, 4287.
[136] Sabelle, S.; Hydrio, J.; Leclerc, E.; Mioskowski, C.; Renard, P.–Y. *Tetrahedron Lett.* **2002**, *43*, 3645.
[137] Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519.
[138] Talukdar, S.; Nayak, S. K.; Banerji, A. *Synth. Commun.* **1998**, *28*, 2325.
[139] Baran, J.; Laszlo, P. *Tetrahedron Lett.* **1985**, *26*, 5135.
[140] Muszkat, K. A.; Jakob, A.; Castel, N.; Fischer, E.; Rauch, K.; Lüttke, W. *J. Photochem. Photobiol. A: Chem.* **1991**, *60*, 193.
[141] McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929.
[142] Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.
[143] Paquette, L. A.; Yan, T.-H.; Wells, G. J. *J. Org. Chem.* **1984**, *49*, 3610.
[144] Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* **2006**, *71*, 9873.
[145] Duan, X.-F.; Zeng, J.; Zhang, Z.-B.; Zi, G.-F. *J. Org. Chem.* **2007**, *72*, 10283.
[146] Baumstark, A. L.; McCloskey, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609.
[147] Eguchi, T.; Kano, H.; Arakawa, K.; Kakinuma, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2545.
[148] Jendralla, H. *Tetrahedron Lett.* **1982**, *23*, 3657.
[149] Hu, Z.; Atwood, J. L.; Cava, M. P. *J. Org. Chem.* **1994**, *59*, 8071.
[150] Grützmacher, H.-F.; Nolte, G. *Chem. Ber.* **1994**, *127*, 1157.
[151] Dai, W.-M.; Mak, W. L. *Tetrahedron Lett.* **2000**, *41*, 10277.
[152] Kuzuhara, D.; Mack, J.; Yamada, H.; Okujima, T.; Ono, N.; Kobayashi, N. *Chem.—Eur. J.* **2009**, *15*, 10060.
[153] Rieke, R. D.; Bales, S. E.; Hudnall, P. M.; Burns, T. P.; Poindexter, G. S. *Org. Synth. Coll. Vol. 6*, **1988**, 845.
[154] Geluk, H. W. *Synthesis* **1970**, 652.
[155] De Selms R. C.; Fox, C. J.; Riordan, R. C. *Tetrahedron Lett.* **1970**, 781.
[156] Newman, M. S.; Sujeeth, P. K. *J. Org. Chem.* **1978**, *43*, 4367.
[157] Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
[158] Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557.
[159] Matsubara, S.; Oshima, K. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley–VCH: Weinheim, 2004, pp 200–222.
[160] Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.
[161] Takai, K.; Fujimura, O.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 211.
[162] Takai, K.; Tezuka, M.; Kataoka, Y.; Utimoto, K. *Synlett* **1989**, 27.
[163] Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.
[164] Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.
[165] Shono, T.; Nagasawa, T.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2007**, *48*, 3521.
[166] Shono, T.; Ito, K.; Tsubouchi, A.; Takeda, T. *Org. Biomol. Chem.* **2005**, *3*, 2914.
[167] Takeda, T.; Tsubouchi, A. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley–VCH: Weinheim, 2004, pp 151–159.
[168] Takeda, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 195.
[169] Takeda, T. *Chem. Rec.* **2007**, *7*, 24.
[170] Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.
[171] Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* **1998**, 741.
[172] Takeda, T.; Watanabe, M.; Nozaki, N.; Fujiwara, T. *Chem. Lett.* **1998**, 115.
[173] Takeda, T.; Saito, J.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 5571.
[174] Takeda, T.; Kuroi, S.; Ozaki, M.; Tsubouchi, A. *Org. Lett.* **2004**, *6*, 3207.
[175] Takeda, T.; Ozaki, M.; Kuroi, S.; Tsubouchi, A. *J. Org. Chem.* **2005**, *70*, 4233.
[176] Takeda, T.; Sato, K.; Tsubouchi, A. *Synthesis* **2004**, 1457.
[177] Rahim, M. A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* **1998**, *39*, 2153.
[178] Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *Chem. Commun.* **2001**, 625.
[179] Rahim, M. A.; Fujiwara, T.; Takeda, T. *Synlett* **1999**, 1029.

[180] Takeda, T.; Yatsumonji, Y.; Tsubouchi, A. *Tetrahedron Lett.* **2005**, *46*, 3157.
[181] Lenoir, D. *Chem. Ber.* **1978**, *111*, 411.
[182] Lenoir, D.; Malwitz, D.; Meyer, B. *Tetrahedron Lett.* **1984**, *25*, 2965.
[183] Timberlake, J. W.; Jun, Y. M. *J. Org. Chem.* **1979**, *44*, 4729.
[184] Böhrer, G.; Knorr, R. *Tetrahedron Lett.* **1984**, *25*, 3675.
[185] Frimer, A. A.; Roth, D. *J. Org. Chem.* **1979**, *44*, 3882.
[186] de Meijere, A.; Wenck, H.; Zöllner, S.; Merstetter, P.; Arnold, A.; Gerson, F.; Schreiner, P. R.; Boese, R.; Bläser, D.; Gleiter, R.; Kozhushkov, S. I. *Chem.-Eur. J.* **2001**, *7*, 5382.
[187] Oelgemöller, M.; Brem, B.; Frank, R.; Schneider, S.; Lenoir, D.; Hertkorn, N.; Origane, Y.; Lemmen, P.; Lex, J.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1760.
[188] Laali, K. K.; Okazaki, T.; Bunge, S. D.; Lenoir, D. *J. Org. Chem.* **2008**, *73*, 4092.
[189] Seo, J. W.; Kim, H. J.; Lee, B. S.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* **2008**, *73*, 715.
[190] Marchand, A. P.; Reddy, G. M.; Deshpande, M. N.; Watson, W. H.; Nagl, A.; Lee, O. S.; Osawa, E. *J. Am. Chem. Soc.* **1990**, *112*, 3521.
[191] Marchand, A. P.; Sorokin, V. D.; Watson, W. H.; Carlson, T. F.; Krawiec, M. *Struct. Chem.* **1994**, *5*, 367.
[192] Marchand, A. P.; Zope, A.; Zaragoza, F.; Bott, S. G.; Ammon, H. L.; Du, Z. *Tetrahedron* **1994**, *50*, 1687.
[193] Watson, W. H.; Nagl, A.; Marchand, A. P.; Deshpande, M. N. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1989**, *45*, 1339.
[194] Gleiter, R.; Borzyk, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1001.
[195] Gleiter, R.; Fritzsche, G.; Borzyk, O.; Oeser, T.; Rominger, F.; Irngartinger, H. *J. Org. Chem.* **1998**, *63*, 2878.
[196] Burgstahler, A. W.; Jahansouz, H.; Véliz, E. A.; Takasugawa, F. *Chirality* **2002**, *14*, 180.
[197] Hünig, S.; Ort, B. *Liebigs Ann. Chem.* **1984**, 1905.
[198] Czekelius, C.; Hafer, J.; Tonzetich, Z. J.; Schrock, R. R.; Christensen, R. L.; Müeller, P. *J. Am. Chem. Soc.* **2006**, *128*, 16664.
[199] Nguyen, T.–T.; Gouriou, Y.; Sallé, M.; Frère, P.; Jubault, M.; Gorgues, A.; Toupet, L.; Riou, A. *Bull. Soc. Chim. Fr.* **1996**, *133*, 301.
[200] Janssen, J.; Lüttke, W. *Chem. Ber.* **1982**, *115*, 1234.
[201] Valla, A.; Valla, B.; Le Guillou, R.; Cartier, D.; Dufossé, L.; Labia, R. *Helv. Chim. Acta* **2007**, *90*, 512.
[202] Broszeit, G.; Diepenbrock, F.; Gräf, O.; Hecht, D.; Heinze, J.; Martin, H.-D.; Mayer, B.; Schaper, K.; Smie, A.; Strehblow, H.-H. *Liebigs Ann./Recl.* **1997**, 2205.
[203] Valla, A. R.; Cartier, D. L.; Valla, B. G.; Le Guillou, R. Y.; Andriamialisoa, Z. R.; Labia, R.; Breithaupt, D. E.; Savy, S. M.; Binet, A.; Dufossé, L. H. *Helv. Chim. Acta* **2003**, *86*, 3314.
[204] Doering, W. von E.; Sarma, K. *J. Am. Chem. Soc.* **1992**, *114*, 6037.
[205] Wang, Y.-P.; Lui, X.-H.; Lin, B.-S.; Tang, W.-D.; Lin, T.-S.; Liaw, J.-H.; Wang, Y.; Liu, Y.-H. *J. Organomet. Chem.* **1999**, *575*, 310.
[206] Bildstein, B.; Denifl, P.; Wurst, K.; André, M.; Baumgarten, M.; Friedrich, J.; Ellmerer-Müller, E. *Organometallics* **1995**, *14*, 4334.
[207] Adams, C. M.; Holt, E. M. *Organometallics* **1990**, *9*, 980.
[208] Toullec, P.; Ricard, L.; Mathey, F. *Organometallics* **2002**, *21*, 2635.
[209] Cheng, J.; Sekher, P.; Singh, S. P.; Gano, J. E.; Morgan, A. R. *Synth. Commun.* **1997**, *27*, 673.
[210] Xie, H.; Lee, D. A.; Wallace, D. M.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1996**, *61*, 8508.
[211] Cheng, J.; Gano, J. E.; Morgan, A. R. *Tetrahedron Lett.* **1996**, *37*, 2721.
[212] Windscheif, P.-M.; Vögtle, F. *Synthesis* **1994**, 87.
[213] Newkome, G. R.; Roper, J. M. *J. Org. Chem.* **1979**, *44*, 502.
[214] Senge, M. O.; Vicente, M. G. H.; Gerzevske, K. R.; Forsyth, T. P.; Smith, K. M. *Inorg. Chem.* **1994**, *33*, 5625.
[215] Graça, M.; Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **1991**, *56*, 4407.
[215a] Graça, M.; Vicente, H.; Rezzano, I. N.; Smith, K. M. *Tetrahedron Lett.* **1990**, *31*, 1365.
[216] Collis, G. E.; Burrell, A. K.; Blandford, E. J.; Officer, D. L. *Tetrahedron* **2007**, *63*, 11141.

[217] Licandro, E.; Rigamonti, C.; Ticozzelli, M. T.; Monteforte, M.; Baldoli, C.; Giannini, C.; Maiorana, S. *Synthesis* **2006**, 3670.
[218] Elandaloussi, E. H.; Frère, P.; Richomme, P.; Orduna, J.; Garin, J.; Roncali, J. *J. Am. Chem. Soc.* **1997**, *119*, 10774.
[219] Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1984**, *106*, 723.
[220] McMurry, J. E.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 10167.
[221] Nakazaki, M.; Yamamoto, K.; Maeda, M.; Sato, O.; Tsutsui, T. *J. Org. Chem.* **1982**, *47*, 1435.
[222] Dressel, J.; Chasey, K. L.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5479.
[223] McMurry, J. E.; Swenson, R. *Tetrahedron Lett.* **1987**, *28*, 3209.
[224] Lee, W. Y.; Park, C. H.; Kim, Y. D. *J. Org. Chem.* **1992**, *57*, 4074.
[225] Vogel, E.; Püttmann, W.; Duchatsch, W.; Schieb, T.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 720.
[226] Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 395.
[227] Hopf, H.; Krüger, A. *Chem.—Eur. J.* **2001**, *7*, 4378.
[228] Eckhardt, M.; Brückner, R. *Liebigs Ann./Recl.* **1997**, 947.
[229] Ojima, J.; Yamamoto, K.; Kato, T.; Wada, K.; Yoneyama, Y.; Ejiri, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2209.
[230] McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Van Duyne, G.; Gleiter, R.; Schäfer, W.; White, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 2932.
[231] McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Mitchell, J. *J. Am. Chem. Soc.* **1986**, *108*, 515.
[232] Esser, B.; Bandyopadhyay, A.; Rominger, F.; Gleiter, R. *Chem.—Eur. J.* **2009**, *15*, 3368.
[233] Dyker, G.; Körning, J.; Stirner, W. *Eur. J. Org. Chem.* **1998**, 149.
[234] Grützmacher, H.-F.; Neumann, E.; Ebmeyer, F.; Albrecht, K.; Schelenz, P. *Chem. Ber.* **1989**, *122*, 2291.
[235] Hopf, H.; Mlynek, C. *J. Org. Chem.* **1990**, *55*, 1361.
[236] Debroy, P.; Lindeman, S. V.; Rathore, R. *J. Org. Chem.* **2009**, *74*, 2080.
[237] Rajakumar, P.; Selvam, S. *Tetrahedron* **2007**, *63*, 8891.
[238] Buretea, M. A.; Tilley, T. D. *Organometallics* **1997**, *16*, 1507.
[239] Shimizu, I.; Kamei, Y.; Tezuka, T.; Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 192.
[240] Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron* **1995**, *51*, 7951.
[241] Lhoták, P.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 645.
[242] Jaiyu, A.; Rojanathanes, R.; Sukwattanasinitt, M. *Tetrahedron Lett.* **2007**, *48*, 1817.
[243] Some, S.; Dutta, B.; Ray, J. K. *Tetrahedron Lett.* **2006**, *47*, 1221.
[244] Yamamoto, K.; Harada, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M.; Kai, Y.; Nakao, T.; Tanaka, M.; Harada, S.; Kasai, N. *J. Am. Chem. Soc.* **1988**, *110*, 3578.
[245] Tanaka, K.; Suzuki, H.; Osuga, H. *J. Org. Chem.* **1997**, *62*, 4465.
[246] Miyasaka, M.; Rajca, A.; Pink, M.; Rajca, S. *Chem.—Eur. J.* **2004**, *10*, 6531.
[247] Berlage, U.; Schmidt, J.; Peters, U.; Welzel, P. *Tetrahedron Lett.* **1987**, *28*, 3091.
[248] Disanayaka, B. W.; Weedon, A. C. *J. Org. Chem.* **1987**, *52*, 2905.
[249] Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057.
[250] Hu, T.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2441.
[251] Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018.
[252] Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2003**, *44*, 3035.
[253] Rajendran, V.; Rong, S.-B.; Saxena, A.; Doctor, B. P.; Kozikowski, A. P. *Tetrahedron Lett.* **2001**, *42*, 5359.
[254] Koft, E. R.; Broadbent, T. A. *Org. Prep. Proced. Int.* **1988**, *20*, 199.
[255] Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369.
[256] Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804.
[257] Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948.
[258] Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5229.

[259] Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905.
[260] Dauben, W. G.; Farkas, I.; Bridon, D. P.; Chuang, C.-P.; Henegar, K. E. *J. Am. Chem. Soc.* **1991**, *113*, 5883.
[261] Nicolaou, K. C.; Yang, Z.; Liu, J.–J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645.
[262] Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513.
[263] Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075.
[264] Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615.
[265] McMurry, J. E.; Bosch, G. K. *Tetrahedron Lett.* **1985**, *26*, 2167.
[266] McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885.
[267] Cane, D. E.; Tsantrizos, Y. S. *J. Am. Chem. Soc.* **1996**, *118*, 10037.
[268] McMurry, J. E.; KočovskÁ, P. *Tetrahedron Lett.* **1985**, *26*, 2171.
[269] Dauben, W. G.; Lorenz, K. L.; Dean, D. W.; Shapiro, G.; Farkas, I. *Tetrahedron Lett.* **1998**, *39*, 7079.
[270] McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723.
[271] Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907.
[272] Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3393.
[273] Li, W.; Li, Y.; Li, Y.-L. *Sci. China Ser. B* **1993**, *36*, 1161.
[274] Mao, J.–M.; Li, Y.; Hou, Z.–J.; Li, Y.-L.; Liang, X.-T. *Sci. China Ser. B* **1992**, *35*, 257.
[275] Li, W.; Li, Y.; Li, Y. *Synth. Commun.* **1992**, *22*, 817.
[276] Li, Y.; Li, W.; Li, Y. L. *Synth. Commun.* **1994**, *24*, 721.
[277] Liu, Z.; Li, W. Z.; Li, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 95.
[278] Yue, X.; Li, Y. *Synthesis* **1996**, 736.
[279] Li, Y.; Liu, Z.; Lan, J.; Li, J.; Peng, L.; Li, W. Z.; Li, Y.; Chan, A. S. C. *Tetrahedron Lett.* **2000**, *41*, 7465.
[280] Li, Y.; Li, W.; Li, Y. *Tetrahedron Lett.* **1992**, *33*, 1225.
[281] Liu, Z.; Zhang, T.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 275.
[282] Xing, Y.; Cen, W.; Lan, J.; Li, Y.; Li, Y. *J. Chin. Chem. Soc. (Taipei, Taiwan)* **1999**, *46*, 595.
[283] Zhang, T.; Liu, Z.; Li, Y. *Synthesis* **2001**, 393.
[284] Li, W.-D.; Li, Y.; Li, Y. *Tetrahedron Lett.* **1999**, *40*, 965.
[285] Li, W.; Mao, J.; Li, Y.; Li, Y. *Org. Prep. Proced. Int.* **1994**, *26*, 445.
[286] Dauben, W. G.; Wang, T.-Z.; Stephens, R. W. *Tetrahedron Lett.* **1990**, *31*, 2393.
[287] Li, J.; Yue, X.; Li, Y.; Hou, L.; Li, W.; Li, Y. *Bull. Soc. Chim. Belg.* **1996**, *105*, 297.
[288] Lan, J.; Liu, Z.; Li, Y.; Cen, W.; Xing, Y. *J. Chin. Chem. Soc. (Taipei, Taiwan)* **1999**, *46*, 941.
[289] Liu, Z.; Peng, L.; Li, W. Z.; Li, Y. *Synlett* **2003**, 1977.
[290] McMurry, J.; Matz, J. R.; Kees, K. L.; Bock, P. A. *Tetrahedron Lett.* **1982**, *23*, 1777.
[291] McMurry, J. E.; Matz, J. R.; Kees, K. L. *Tetrahedron* **1987**, *43*, 5489.
[292] Mermet-Mouttet, M. P.; Gabriel, K.; Heissler, D. *Tetrahedron Lett.* **1999**, *40*, 843.
[293] Brown, R. F. C.; Robinson, A. J. *Aust. J. Chem.* **1995**, *48*, 515.
[294] Maercker, A. *Org. React.* **1965**, *14*, 270.
[295] Wadsworth, Jr., W. S. *Org. React.* **1977**, *25*, 73.
[296] Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049.
[297] Bégúe, J. P.; Bonnet Delpon, D.; Wu, S.–W.; M'bida, A.; Shintani, T.; Nakai, T. *Tetrahedron Lett.* **1994**, *35*, 2907.
[298] Kraus, G. A.; Shi, J. *J. Org. Chem.* **1991**, *56*, 4147.
[299] Ager, D. J. *Org. React.* **1990**, *38*, 1.
[300] Kano, N.; Kawashima, T. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley–VCH: Weinheim, 2004, pp 18–103.
[301] Kocienski, P. J. *Chem. Ind. (London)* **1981**, 548.
[302] Kocienski, P. *Phosphorus, Sulfur Relat. Elem.* **1985**, *24*, 97.
[303] Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
[304] Dumeunier, R.; Marko, I. E. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley–VCH: Weinheim, 2004, pp 104–150.

[305] Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831.
[306] Schrock, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 5399.
[307] Pine, S. H. *Org. React.* **1993**, *43*, 1.
[308] Petasis, N. A. In *Transition Metals for Organic Synthesis (2nd Edition)*; Beller, M.; Bolm, C., Eds.; Wiley–VCH: Weinheim, 2004, pp 427–447.
[309] Petasis, N. A.; Lu, S.–P.; Bzowej, E. I.; Fu, D.–K.; Staszewski, J. P.; Akritopoulou–Zanze, I.; Patane, M. A.; Hu, Y. H. *Pure Appl. Chem.* **1996**, *68*, 667.
[310] Takai, K. *Org. React.* **2004**, *64*, 253.
[311] Chen, J.; Li, J.; Yu, M.-h.; Chen, W.-x.; Fu, H.–l. *Org. Prep. Proced. Int.* **1997**, *29*, 569.
[312] Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1991**, *56*, 1940.
[313] Bolton, R.; Luff, S.; Sutcliffe, L. H. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 1205.
[314] Kawase, T.; Ueda, N.; Tanaka, K.; Seirai, Y.; Oda, M. *Tetrahedron Lett.* **2001**, *42*, 5509.
[315] Chen, H.–B.; Yin, J.; Wang, Y.; Pei, J. *Org. Lett.* **2008**, *10*, 3113.
[316] Murata, M.; Maeda, S.; Morinaka, Y.; Murata, Y.; Komatsu, K. *J. Am. Chem. Soc.* **2008**, *130*, 15800.
[317] Stuhr-Hansen, N. *Tetrahedron Lett.* **2005**, *46*, 5491.
[318] Yamamoto, T.; Takimiya, K. *J. Am. Chem. Soc.* **2007**, *129*, 2224.
[319] Meier, H.; Rose, B.; Schollmeyer, D. *Liebigs Ann./Recl.* **1997**, 1173.
[320] Hughes, R. P.; Kowalski, A. S.; Lomprey, J. R.; Neithamer, D. R. *J. Org. Chem.* **1996**, *61*, 401.
[321] Begley, M. J.; Pattenden, G.; Robertson, G. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1085.
[322] Li, W.; Li, Y.; Li, Y. L. *Synthesis* **1994**, 267.
[323] Elandaloussi, E. H.; Frère, P.; Benahmed-Gasmi, A.; Riou, A.; Gorgues, A.; Roncali, J. *J. Mater. Chem.* **1996**, *6*, 1859.
[324] Nakayama, J.; Murabayashi, S.; Hoshino, M. *Heterocycles* **1986**, *24*, 2639.
[325] Starčević, K.; Boykin, D. W.; Karminski-Zamola, G. *Heteroat. Chem.* **2003**, *14*, 218.
[326] Nakayama, J.; Fujimori, T. *Heterocycles* **1991**, *32*, 991.
[327] Chen, R.; Yang, X.; Tian, H.; Wang, X.; Hagfeldt, A.; Sun, L. *Chem. Mater.* **2007**, *19*, 4007.
[328] Yamamoto, T.; Miyazaki, E.; Takimiya, K. *Heterocycles* **2008**, *76*, 583.
[329] Akoudad, S.; Frère, P.; Mercier, N.; Roncali, J. *J. Org. Chem.* **1999**, *64*, 4267.
[330] Harwood, L. M.; Jones, G.; Pickard, J.; Thomas, R. M.; Watkin, D. *Tetrahedron Lett.* **1988**, *29*, 5825.
[331] Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1990**, *43*, 1439.
[332] Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1991**, 1432.
[333] Talukdar, S.; Nayak, S. K.; Banerji, A. *Fullerene Sci. Technol.* **1995**, *3*, 327.
[334] Zhang, W.; Go, M. L. *Eur. J. Med. Chem.* **2007**, *42*, 841.
[335] Warren, S.; Wyatt, P.; McPartlin, M.; Woodroffe, T. *Tetrahedron Lett.* **1996**, *37*, 5609.
[336] Warren, S.; Wyatt, P. *Tetrahedron: Asymmetry* **1996**, *7*, 989.
[337] Létard, J.-F.; Lapouyade, R.; Rettig, W. *Chem. Phys. Lett.* **1994**, *222*, 209.
[338] Sigalov, M.; Ben-Asuly, A.; Shapiro, L.; Ellern, A.; Khodorkovsky, V. *Tetrahedron Lett.* **2000**, *41*, 8573.
[339] Tanner, D.; Johansson, F.; Harden, A.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 15731.
[340] Wang, X.; Zhou, G.; Wang, D.; Wang, C.; Fang, Q.; Jiang, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1977.
[341] Afonso, C. A. M.; Motherwell, W. B.; O'Shea, D. M.; Roberts, L. R. *Tetrahedron Lett.* **1992**, *33*, 3899.
[342] Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.
[343] Bhatt, S.; Nayak, S. K. *Tetrahedron Lett.* **2009**, *50*, 5823.
[344] Hirsenkorn, R. *Tetrahedron Lett.* **1990**, *31*, 7591.
[345] Cheng, J.-C.; Fang, J.-G.; Chen, W.-F.; Zhou, B.; Yang, L.; Liu, Z.–L. *Bioorg. Chem.* **2006**, *34*, 142.
[346] Shadakshari, U.; Rele, S.; Nayak, S. K.; Chattopadhyay, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 1934.
[347] Guha, P.; Dey, A.; Sarkar, B.; Dhyani, M. V.; Chattopadhyay, S.; Bandyopadhyay, S. K. *J. Pharmacol. Exp. Ther.* **2009**, *328*, 829.

[348] Wyatt, P.; Warren, S.; McPartlin, M.; Woodroffe, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 279.
[349] Castedo, L.; Saá, J. M.; Suau, R.; Tojo, G. *J. Org. Chem.* **1981**, *46*, 4292.
[350] Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1130.
[351] Schertl, S.; Hartmann, R. W.; Batzl-Hartmann, C.; Schlemmer, R.; Spruss, T.; Bernhardt, G.; Gust, R.; Schönenberger, H. *Arch. Pharm. (Weinheim)* **2001**, *334*, 125.
[352] Subramanian, M.; Shadakshari, U.; Chattopadhyay, S. *Bioorg. Med. Chem.* **2004**, *12*, 1231.
[353] Donnoli, M. I.; Scafato, P.; Superchi, S.; Rosini, C. *Chirality* **2001**, *13*, 258.
[354] Lindsten, G.; Wennerström, O.; Thulin, B. *Acta Chem. Scand. Ser. B* **1986**, *40*, 545.
[355] Snider, B. B.; Jackson, A. C. *J. Org. Chem.* **1983**, *48*, 1471.
[356] Maeda, H.; Nishimura, K.; Mizuno, K.; Yamaji, M.; Oshima, J.; Tobita, S. *J. Org. Chem.* **2005**, *70*, 9693.
[357] Boeré, R. T.; Robbins, S. J. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2008**, *E64*, o363.
[358] Witiak, D. T.; Kamat, P. L.; Allison, D. L.; Liebowitz, S. M.; Glaser, R.; Holliday, J. E.; Moeschberger, M. L.; Schaller, J. P. *J. Med. Chem.* **1983**, *26*, 1679.
[359] Peeters, E.; van Hal, P. A.; Knol, J.; Brabec, C. J.; Sariciftci, N. S.; Hummelen, J. C.; Janssen, R. A. J. *J. Phys. Chem. B* **2000**, *104*, 10174.
[360] Zimmerman, H. E.; Kamath, A. P. *J. Am. Chem. Soc.* **1988**, *110*, 900.
[361] Gapski, G.; Kini, A.; Liu, R. S. H. *Chem. Lett.* **1978**, 803.
[362] Fritsch, R.; Hartmann, E.; Andert, D.; Mannschreck, A. *Chem. Ber.* **1992**, *125*, 849.
[363] Mannschreck, A.; Hartmann, E.; Buchner, H.; Andert, D. *Tetrahedron Lett.* **1987**, *28*, 3479.
[364] Saltiel, J.; Wang, S. *Photochem. Photobiol. Sci.* **2006**, *5*, 883.
[365] Ray, J. K.; Gupta, S.; Raj, S. S. S.; Fun, H.-K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *C55*, 1847.
[366] Wallace, R. H.; Lu, Y.; Liu, J.; Atwood, J. L. *Synlett* **1992**, 992.
[367] Mallory, F. B.; Butler, K. E.; Bérubé, A.; Luzik, Jr., E. D.; Mallory, C. W.; Brondyke, E. J.; Hiremath, R.; Ngo, P.; Carroll, P. J. *Tetrahedron* **2001**, *57*, 3715.
[368] Bringmann, G.; Pabst, T.; Henschel, P.; Michel, M. *Tetrahedron* **2001**, *57*, 1269.
[369] Merz, A.; Gromann, L.; Karl, A.; Parkanyi, L.; Schneider, O. *Eur. J. Org. Chem.* **1998**, 403.
[370] Maiorana, S.; Papagni, A.; Licandro, E.; Annunziata, R.; Paravidino, P.; Perdicchia, D.; Giannini, C.; Bencini, M.; Clays, K.; Persoons, A. *Tetrahedron* **2003**, *59*, 6481.
[371] Lee, H.-J.; Noh, D.-Y. *Synth. Met.* **1999**, *102*, 1696.
[372] Neidlein, R.; Winkler, R. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2258.
[373] Agustsson, S. O.; Hu, C.; Englert, U.; Marx, T.; Wesemann, L.; Ganter, C. *Organometallics* **2002**, *21*, 2993.
[374] Ishii, T.; Sawada, T.; Mataka, S.; Tashiro, M.; Thiemann, T. *Chem. Ber.* **1996**, *129*, 289.
[375] Simokaitiene, J.; Grigalevicius, S.; Grazulevicius, J. V.; Rutkaite, R.; Kazlauskas, K.; Jursenas, S.; Jankauskas, V.; Sidaravicius, J. *J. Optoelectron. Adv. Mater.* **2006**, *8*, 876.
[376] Chen, C.-H.; Lin, J. T.; Yeh, M.-C. P. *Tetrahedron* **2006**, *62*, 8564.
[377] Song, Y.; Di, C.-a.; Wei, Z.; Zhao, T.; Xu, W.; Liu, Y.; Zhang, D.; Zhu, D. *Chem.-Eur. J.* **2008**, *14*, 4731.
[378] Elandaloussi, E. H.; Frère, P.; Roncali, J. *Tetrahedron Lett.* **1996**, *37*, 6121.
[379] Mandai, T.; Yamaguchi, H.; Nishikawa, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1981**, *22*, 763.
[380] Stuhr-Hansen, N.; Christensen, J. B.; Harrit, N.; Bjørnholm, T. *J. Org. Chem.* **2003**, *68*, 1275.
[381] Cravey, M. J.; Doss, D. J. *J. Org. Chem.* **1988**, *53*, 5963.
[382] Hu, Y.; Wex, B.; Perkovic, M. W.; Neckers, D. C. *Tetrahedron* **2008**, *64*, 2251.
[383] Larsen, J.; Bechgaard, K. *Acta Chem. Scand.* **1996**, *50*, 71.
[384] Märkl, G.; Aschenbrenner, N.; Baur, A.; Rastorfer, C.; Kreitmeier, P. *Helv. Chim. Acta* **2003**, *86*, 2589.
[385] Jestin, I.; Frère, P.; Blanchard, P.; Roncali, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 942.
[386] Jestin, I.; Frère, P.; Mercier, N.; Levillain, E.; Stievenard, D.; Roncali, J. *J. Am. Chem. Soc.* **1998**, *120*, 8150.

[387] Oswald, F.; Islam, D.–M. S.; Araki, Y.; Troiani, V.; de la Cruz, P.; Moreno, A.; Ito, O.; Langa, F. *Chem.—Eur. J.* **2007**, *13*, 3924.
[388] Ono, N.; Okumura, H.; Murashima, T. *Heteroat. Chem.* **2001**, *12*, 414.
[389] Thomas, K. R. J.; Lin, J. T.; Wen, Y. S. *Organometallics* **2000**, *19*, 1008.
[390] Jung, M. E.; Liu, C.-Y. *J. Org. Chem.* **1986**, *51*, 5446.
[391] Tsuge, A.; Nishimoto, T.; Uchida, T.; Yasutake, M.; Moriguchi, T.; Sakata, K. *J. Org. Chem.* **1999**, *64*, 7246.
[392] Siutkowski, M.; Mercier, F.; Ricard, L.; Mathey, F. *Organometallics* **2006**, *25*, 2585.
[393] Blanchard, P.; Verlhac, P.; Michaux, L.; Frére, P.; Roncali, J. *Chem.—Eur. J.* **2006**, *12*, 1244.
[394] Paolesse, R.; Pandey, R. K.; Forsyth, T. P.; Jaquinod, L.; Gerzevske, K. R.; Nurco, D. J.; Senge, M. O.; Licoccia, S.; Boschi, T.; Smith, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3869.
[395] Pandey, R. K.; Forsyth, T. P.; Gerzevske, K. R.; Lin, J. J.; Smith, K. M. *Tetrahedron Lett.* **1992**, *33*, 5315.
[396] Goswami, L. N.; Ethirajan, M.; Dobhal, M. P.; Zhang, M.; Missert, J. R.; Shibata, M.; Kadish, K. M.; Pandey, R. K. *J. Org. Chem.* **2009**, *74*, 568.
[397] Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1013.
[398] Senge, M. O.; Kalisch, W. W.; Ruhlandt-Senge, K. *Chem. Commun.* **1996**, 2149.
[399] Cosmo, R.; Kautz, C.; Meerholz, K.; Heinze, J.; Müllen, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 604.
[400] Wang, J.-L.; Duan, X.-F.; Jiang, B.; Gan, L.-B.; Pei, J.; He, C.; Li, Y.-F. *J. Org. Chem.* **2006**, *71*, 4400.
[401] Gano, J. E.; Lenoir, D.; Park, B.-S.; Roesner, R. A. *J. Org. Chem.* **1987**, *52*, 5636.
[402] Bellucci, G.; Bianchini, R.; Chiappe, C.; Lenoir, D.; Attar, A. *J. Am. Chem. Soc.* **1995**, *117*, 6243.
[403] Doering, W. von E.; Kitagawa, T. *J. Am. Chem. Soc.* **1991**, *113*, 4288.
[404] Doering, W. von E.; Roth, W. R.; Bauer, F.; Breuckmann, R.; Ebbrecht, T.; Herbold, M.; Schmidt, R.; Lennartz, H.-W.; Lenoir, D.; Boese, R. *Chem. Ber.* **1989**, *122*, 1263.
[405] Klein, O.; Hopf, H.; Grunenberg, J. *Eur. J. Org. Chem.* **2009**, 2141.
[406] Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1781.
[407] Sander, M.; Dehmlow, E. V. *Eur. J. Org. Chem.* **2001**, 399.
[408] Zhu, B. L.; Miljanić, O. Š.; Vollhardt, K. P. C.; West, M. J. *Synthesis* **2005**, 3373.
[409] Wang, Y.; Doering, W. von E.; Staples, R. J. *J. Chem. Crystallogr.* **1999**, *29*, 977.
[410] Nelsen, S. F.; Reinhardt, L. A. *J. Phys. Org. Chem.* **2001**, *14*, 847.
[411] Blanchard, P.; Brisset, H.; Illien, B.; Riou, A.; Roncali, J. *J. Org. Chem.* **1997**, *62*, 2401.
[412] Kakiuchi, K.; Okada, H.; Kanehisa, N.; Kai, Y.; Kurosawa, H. *J. Org. Chem.* **1996**, *61*, 2972.
[413] Ayats, C.; Camps, P.; Fernández, J. A.; Vázquez, S. *Chem.—Eur. J.* **2007**, *13*, 1522.
[414] Andersson, P. G. *Tetrahedron Lett.* **1994**, *35*, 2609.
[415] Anke, L.; Reinhard, D.; Weyerstahl, P. *Liebigs Ann. Chem.* **1981**, 591.
[416] Kadam, S. M.; Nayak, S. K.; Banerji, A. *Synth. Commun.* **1995**, *25*, 135.
[417] Richardson, W. H. *Synth. Commun.* **1981**, *11*, 895.
[418] Daik, R.; Feast, W. J.; Batsanov, A. S.; Howard, J. A. K. *New J. Chem.* **1998**, *22*, 1047.
[419] Nayak, S. K.; Banerji, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1991**, *30*, 286.
[420] Bottino, F. A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 77.
[421] Schneider, S.; Brem, B.; Jäger, W.; Rehaber, H.; Lenoir, D.; Frank, R. *Chem. Phys. Lett.* **1999**, *308*, 211.
[422] Besançon, J.; Szymoniak, J.; Moïse, C. *J. Organomet. Chem.* **1992**, *426*, 325.
[423] Amposta, R.; Camps, P.; Figueredo, M.; Jaime, C.; Virgili, A. *An. Quim., Ser. C* **1981**, *77*, 267.
[424] Kochanny, M. J.; Härd, T.; Katzenellenbogen, J. A. *Magn. Reson. Chem.* **1993**, *31*, 977.
[425] Rhee, C. K.; Chae, K.; Levy, L. A.; Korach, K. S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 133.
[426] Chen, W.-X.; Feng, J.-C.; Zhou, Z.-L.; Zhang, J.-H. *Synthesis* **1989**, 182.
[427] De Clercq, P. J.; Van Peteghem, C. H.; Jonckheere, J. A.; Deleenheer, A. P. *J. Labelled Compd. Radiopharm.* **1984**, *21*, 649.
[428] McLachlan, J. A.; Baucom, K.; Korach, K. S.; Levy, L.; Metzler, M. *Steroids* **1979**, *33*, 543.

[429] Khoury, R. G.; Jaquinod, L.; Smith, K. M. *Chem. Commun.* **1997**, 1057.
[430] Lenoir, D.; Lemmen, P. *Chem. Ber.* **1980**, *113*, 3112.
[431] Saltiel, J.; Mace, J. E.; Watkins, L. P.; Gormin, D. A.; Clark, R. J.; Dmitrenko, O. *J. Am. Chem. Soc.* **2003**, *125*, 16158.
[432] Lemmen, P.; Lenoir, D. *Chem. Ber.* **1984**, *117*, 2300.
[433] Tolstikov, G. A.; Lerman, B. M.; Belogaeva, T. A. *Synth. Commun.* **1991**, *21*, 877.
[434] Doering, W. von E.; Birladeanu, L.; Cheng, X.-H.; Kitagawa, T.; Sarma, K. *J. Am. Chem. Soc.* **1991**, *113*, 4558.
[435] Wenck, H.; de Meijere, A.; Gerson, F.; Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 335.
[436] Hwang, K.–J.; Carlson, K. E.; Anstead, G. M.; Katzenellenbogen, J. A. *Biochemistry* **1992**, *31*, 11536.
[437] Olah, G. A.; Prakash, G. K. S. *J. Org. Chem.* **1977**, *42*, 580.
[438] Nickon, A.; Zurer, P. St. Jr.; Hrnjez, B.; Tino, J. *Tetrahedron* **1983**, *39*, 2679.
[439] Doering, W. von E.; Shi, Y.-q.; Zhao, D.-c. *J. Am. Chem. Soc.* **1992**, *114*, 10763.
[440] Doering, W. von E.; Birladeanu, L.; Sarma, K.; Shao, L.-S. *J. Am. Chem. Soc.* **1996**, *118*, 6660.
[441] Yamamoto, K.; Ojima, J.; Morita, N.; Asao, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1281.
[442] Yamamoto, K.; Ojima, J.; Morita, N.; Asao, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1851.
[443] Olah, G. A.; Prakash, G. K. S.; Liang, G. *Synthesis* **1976**, 318.
[444] Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G.; Stratakis, M. *Org. Lett.* **2005**, *7*, 2357.
[445] Ikeda, H.; Sakai, A.; Namai, H.; Kawabe, A.; Mizuno, K. *Tetrahedron Lett.* **2007**, *48*, 8338.
[446] Shimasaki, T.; Kato, S.; Shinmyozu, T. *J. Org. Chem.* **2007**, *72*, 6251.
[447] Blanchard, P.; Riou, A.; Roncali, J. *J. Org. Chem.* **1998**, *63*, 7107.
[448] Vögtle, F.; Thilgen, C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1162.
[449] Cory, R. M.; Walker, J. R.; Zabel, P. D. *Synth. Commun.* **1994**, *24*, 799.
[450] Blanchard, P.; Brisset, H.; Riou, A.; Hierle, R.; Roncali, J. *J. Org. Chem.* **1998**, *63*, 8310.
[451] Blanchard, P.; Brisset, H.; Riou, A.; Hierle, R.; Roncali, J. *New J. Chem.* **1998**, *22*, 547.
[452] Laatsch, H.; Talvitie, A.; Kral, A.; Ernst, B.-P.; Moltemeyer, M. *J. Prakt. Chem.-Chem. Ztg.* **1996**, *338*, 140.
[453] Anderson, J. E.; Bettels, B. R. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1121.
[454] Pollard, M. M.; Meetsma, A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 507.
[455] Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.
[456] Chen, Y. J.; Pan, D.-S.; Chiu, C.-F.; Su, J.-X.; Lin, S. J.; Kwan, K. S. *Inorg. Chem.* **2000**, *39*, 953.
[457] Chiu, C.-F.; Song, M.; Chen, B.-H.; Kwan, K. S. *Inorg. Chim. Acta* **1997**, *266*, 73.
[458] Gano, J. E.; Osborn, III, D. J.; Kodali, N.; Sekher, P.; Liu, M.; Luzik, E. D. *J. Org. Chem.* **2003**, *68*, 3710.
[459] Columbus, I.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 3402.
[460] Columbus, I.; Biali, S. E. *Chirality* **1998**, *10*, 159.
[461] Tong, H.; Hong, Y. N.; Dong, Y.; Häußler, M.; Li, Z.; Lam, J. W. Y.; Dong, Y. P.; Sung, H. H. Y.; Williams, I. D.; Tang, B. Z. *J. Phys. Chem. B* **2007**, *111*, 11817.
[462] Chung, M.-K.; Fancy, P.; Stryker, J. M. *Can. J. Chem.* **2006**, *84*, 1250.
[463] Kuntz, J.-F.; Schneider, R.; Walcarius, A.; Fort, Y. *Tetrahedron Lett.* **2005**, *46*, 8793.
[464] Hong, Y.; Häußler, M.; Lam, J. W. Y.; Li, Z.; Sin, K. K.; Dong, Y; Tong, H.; Liu, J.; Qin, A.; Renneberg, R.; Tang, B. Z. *Chem.—Eur. J.* **2008**, *14*, 6428.
[465] Schreivogel, A.; Maurer, J.; Winter, R.; Baro, A.; Laschat, S. *Eur. J. Org. Chem.* **2006**, 3395.
[466] Schultz, A.; Diele, S.; Laschat, S.; Nimtz, M. *Adv. Funct. Mater.* **2001**, *11*, 441.
[467] Hussain, Z.; Hopf, H.; Oeser, T. *Lett. Org. Chem.* **2005**, *2*, 518.
[468] Schultz, A.; Laschat, S.; Diele, S.; Nimtz, M. *Eur. J. Org. Chem.* **2003**, 2829.
[469] Chung, M.-K.; Qi, G.; Stryker, J. M. *Org. Lett.* **2006**, *8*, 1491.
[470] Navale, T. S.; Zhai, L.; Lindeman, S. V.; Rathore, R. *Chem. Commun.* **2009**, 2857.
[471] Fürstner, A.; Hupperts, A.; Seidel, G. *Org. Synth.* **1999,** *76* 142.
[472] Belen'kii, L. I.; Gromova, G. P.; Kolotaev, A. V.; Nabatov, B. V.; Krayushkin, M. M. *Russ. Chem. Bull.* **2005**, *54*, 1208.

[473] Halvorsen, H.; Skramstad, J.; Hope, H. *Synth. Commun.* **2007**, *37*, 1179.
[474] Larsen, J.; Bechgaard, K. *Acta Chem. Scand.* **1996**, *50*, 77.
[475] Rathore, R.; Lindeman, S. V.; Kumar, A. S.; Kochi, J. K. *J. Am. Chem. Soc.* **1998**, *120*, 6931.
[476] ter Wiel, M. K. J.; Koumura, N.; van Delden, R. A.; Meetsma, A.; Harada, N.; Feringa, B. L. *Chirality* **2000**, *12*, 734.
[477] ter Wiel, M. K. J.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 15076.
[478] ter Wiel, M. K. J.; Feringa, B. L. *Synthesis* **2005**, 1789.
[479] Harada, N.; Saito, A.; Koumura, N.; Uda, H.; deLange, B.; Jager, W. F.; Wynberg, H.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7241.
[480] Schwager, H.; Wilke, G. *Chem. Ber.* **1987**, *120*, 79.
[481] Dang, Y.; Geise, H.; Dommisse, R.; Esmans, E. *Inorg. Chim. Acta* **1990**, *175*, 115.
[482] Lorcy, D.; Rault-Berthelot, J.; Poriel, C. *Electrochem. Commun.* **2000**, *2*, 382.
[483] Willem, R.; Pepermans, H.; Hallenga, K.; Gielen, M.; Dams, R.; Geise, H. J. *J. Org. Chem.* **1983**, *48*, 1890.
[484] Grützmacher, H.-F.; Husemann, W. *Tetrahedron Lett.* **1985**, *26*, 2431.
[485] Shultz, D. A.; Fox, M. A. *Tetrahedron Lett.* **1988**, *29*, 4377.
[486] Keyes, R. F.; Cushman, M. *Med. Chem. Res.* **1996**, *6*, 372.
[487] Koumura, N.; Osawa, S.; Harada, N. *Enantiomer* **2000**, *5*, 129.
[488] Agranat, I.; Cohen, S.; Isaksson, R.; Sandström, J.; Suissa, M. R. *J. Org. Chem.* **1990**, *55*, 4943.
[489] ter Wiel, M. K. J.; van Delden, R. A.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 14208.
[490] van Delden, R. A.; ter Wiel, M. K. J.; Feringa, B. L. *Chem. Commun.* **2004**, 200.
[491] Tapuhi, Y.; Suissa, M. R.; Cohen, S.; Biedermann, P. U.; Levy, A.; Agranat, I. *J. Chem. Soc. Perkin Trans. 2* **2000**, 93.
[492] Hopf, H.; Kreutzer, M.; Jones, P. G. *Chem. Ber.* **1991**, *124*, 1471.
[493] Jousselme, B.; Blanchard, P.; Frère, P.; Roncali, J. *Tetrahedron Lett.* **2000**, *41*, 5057.
[494] Nützel, R.; Haslinger, E. *Fett. Wiss. Technol.* **1995**, *97*, 137.
[495] Matile, S.; Berova, N.; Nakanishi, K.; Fleischhauer, J.; Woody, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 5198.
[496] Kim, S.–K.; Park, Y.–I.; Park, J.–W. *Mol. Cryst. Liq. Cryst.* **2006**, *458*, 209.
[497] Märkl, G.; Hafner, M.; Kreitmeier, P.; Stadler, C.; Daub, J.; Nöth, H.; Schmidt, M.; Gescheidt, G. *Helv. Chim. Acta* **1997**, *80*, 2456.
[498] Heirtzler, F. R.; Hopf, H.; Jones, P. G.; Bubenitschek, P. *Tetrahedron Lett.* **1995**, *36*, 1239.
[499] Gano, J. E.; Kirschbaum, K.; Luzik, Jr., E. D.; Sekher, P. *Tetrahedron Lett.* **1998**, *39*, 6641.
[500] Kim, S.-K.; Park, Y.-I.; Park, J.-W.; Kim, K.-S.; Choi, C.-K.; Lee, S.-D. *Mol. Cryst. Liq. Cryst.* **2007**, *462*, 209.
[501] Grieser, U.; Hafner, K. *Tetrahedron Lett.* **1994**, *35*, 7759.
[502] Caroli, G.; Kwit, M. G.; Feringa, B. L. *Tetrahedron* **2008**, *64*, 5956.
[503] Khotina, I. A.; Izumrudov, V. A.; Tchebotareva, N. V.; Rusanov, A. L. *Macromol. Chem. Phys.* **2001**, *202*, 2360.
[504] Kim, S.-K.; Park, J.-W.; Oh, S.-Y. *Mol. Cryst. Liq. Cryst.* **2007**, *471*, 89.
[505] Shimasaki, T.; Kato, S.; Ideta, K.; Goto, K.; Shinmyozu, T. *J. Org. Chem.* **2007**, *72*, 1073.
[506] Cao, X.-Y.; Zhang, W.; Zi, H.; Pei, J. *Org. Lett.* **2004**, *6*, 4845.
[507] Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 5482.
[508] Reference deleted.
[509] Li, J.; Liu, Z.; Lan, J.; Li, Y. *J. Chin. Chem. Soc. (Taipei, Taiwan)* **1999**, *46*, 259.
[510] Li, J.; Liu, Z.; Lan, J.; Li, Y. *Chem. Lett.* **1997**, 229.
[511] Seijas, J. A.; de Lera, A. R.; Villaverde, M. C.; Castedo, L. *J. Chem. Soc., Chem. Commun.* **1985**, 839.
[512] De Boeck, B.; Harrington-Frost, N. M.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 340.
[513] De Boeck, B.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 6975.
[514] McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942.

[515] Bonazzola, L.; Michaut, J.–P.; Roncin, J.; Misawa, H.; Sakuragi, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 347.
[516] Feringa, B.; Wynberg, H. *Recl. Trav. Chim. Pay–Bas* **1978**, *97*, 249.
[517] Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, *68*, 9489.
[518] Seo, J. W.; Comninos, J. S.; Chi, D. Y.; Kim, D. W.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **2006**, *49*, 2496.
[519] Ruasse, M.-F.; Motallebi, S.; Galland, B.; Lomas, J. S. *J. Org. Chem.* **1990**, *55*, 2298.
[520] Loza, M. I.; Sanz, F.; Cadavid, M. I.; Honrubia, M.; Orallo, F.; Fontenla, J. A.; Calleja, J. M.; Dot, T.; Manaut, F.; Cid, M. M.; Dominguez, R.; Seijas, J. A.; Villaverde, M. C. *J. Pharm. Sci.* **1993**, *82*, 1090.
[521] Cid, M. M.; Seijas, J. A.; Villaverde, M. C.; Castedo, L. *Tetrahedron* **1988**, *44*, 6197.
[522] Xu, G.; Kannan, A.; Hartman, T. L.; Wargo, H.; Watson, K.; Turpin, J. A.; Buckheit, Jr., R. W.; Johnson, A. A.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2002**, *10*, 2807.
[523] Honrubia, M. A.; Rodriguez, J.; Dominguez, R.; Lozoya, E.; Manaut, F.; Seijas, J. A.; Villaverde, M. C.; Calleja, J. M.; Cadavid, M. I.; Maayani, S.; Sanz, F.; Loza, M. I. *Chem. Pharm. Bull.* **1997**, *45*, 842.
[524] Zhang, X.; Rice, K. C.; Calderon, S. N.; Kayakiri, H.; Smith, L.; Coop, A.; Jacobson, A. E.; Rothman, R. B.; Davis, P.; Dersch, C. M.; Porreca, F. *J. Med. Chem.* **1999**, *42*, 5455.
[525] Gao, M.; Wang, M.; Mock, B. H.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D.; Zheng, Q.-H. *Appl. Radiat. Isot.* **2008**, *66*, 523.
[526] Gärtner, P.; Hofbauer, K.; Reichel, C.; Geisendorfer, T.; Gmeiner, G. *J. Mass Spectrom.* **2008**, *43*, 958.
[527] Pettersson, I.; Berg, U. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1365.
[528] Pettersson, I.; Berg, U. *J. Chem. Res. (S)* **1984**, 208.
[529] Muthyala, R. S.; Sheng, S.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2003**, *46*, 1589.
[530] Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2005**, *13*, 417.
[531] Meegan, M. J.; Hughes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *Anti-Cancer Drug Des.* **2001**, *16*, 57.
[532] Muthyala, R. S.; Carlson, K. E.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4485.
[533] Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1953.
[534] Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2004**, *12*, 5929.
[535] Tanpure, R. P.; Harkrider, A. R.; Strecker, T. E.; Hamel, E.; Trawick, M. L.; Pinney, K. G. *Bioorg. Med. Chem.* **2009**, *17*, 6993.
[536] Zheng, L.; Wei, Q.; Zhou, B.; Yang, L.; Liu, Z.-L. *Anti-Cancer Drugs* **2007**, *18*, 1039.
[537] Richardson, W. H.; Thomson, S. A. *J. Org. Chem.* **1985**, *50*, 1803.
[538] Top, S.; Kaloun, E. B.; Vessières, A.; Laïos, I.; Leclercq, G.; Jaouen, G. *J. Organomet. Chem.* **2002**, *643–644*, 350.
[539] Top, S.; Kaloun, E. B.; Jaouen, G. *J. Am. Chem. Soc.* **2000**, *122*, 736.
[540] Top, S.; Kaloun, E. B.; Toppi, S.; Herrbach, A.; McGlinchey, M. J.; Jaouen, G. *Organometallics* **2001**, *20*, 4554.
[541] Hillard, E. A.; Vessières, A.; Top, S.; Pigeon, P.; Kowalski, K.; Huché, M.; Jaouen, G. *J. Organomet. Chem.* **2007**, *692*, 1315.
[542] Top, S.; Vessières, A.; Pigeon, P.; Rager, M.–N.; Huché, M.; Salomon, E.; Cabestaing, C.; Vaissermann, J.; Jaouen, G. *ChemBioChem* **2004**, *5*, 1104.
[543] Jaouen, G.; Top, S.; Vessiéres, A.; Pigeon, P.; Leclercq, G.; Laios, I. *Chem. Commun.* **2001**, 383.
[544] Pons, J.; Santelli, M. *Tetrahedron* **1990**, *46*, 513.
[545] Schwarz, W.; Hartmann, R. W.; Schönenberger, H. *Arch. Pharm.* **1991**, *324*, 223.
[546] Pigeon, P.; Top, S.; Zekri, O.; Hillard, E. A.; Vessières, A.; Plamont, M.-A.; Buriez, O.; Labbé, E.; Huché, M.; Boutamine, S.; Amatore, C.; Jaouen, G. *J. Organomet. Chem.* **2009**, *694*, 895.
[547] Shi, Y.; Koh, J. T. *ChemBioChem* **2004**, *5*, 788.
[548] Vessiéres, A.; Top, S.; Pigeon, P.; Hillard, E.; Boubeker, L.; Spera, D.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 3937.

[549] Rubin, V. N.; Ruenitz, P. C.; Boudinot, F. D.; Boyd, J. L. *Bioorg. Med. Chem.* **2001**, *9*, 1579.
[550] McGlinchey, M. J.; Nikitin, K.; Ortin, Y.; Müller-Bunz, H.; Plamont, M.-A.; Jaouen, G.; Vessières, A. *J. Organomet. Chem.* **2010**, *695*, 595.
[551] Ruenitz, P. C.; Bourne, C. S.; Sullivan, K. J.; Moore, S. A. *J. Med. Chem.* **1996**, *39*, 4853.
[552] Kraft, K. S.; Ruenitz, P. C.; Bartlett, M. G. *J. Med. Chem.* **1999**, *42*, 3126.
[553] Chao, E. Y. H.; Collins, J. L.; Gaillard, S.; Miller, A. B.; Wang, L.; Orband-Miller, L. A.; Nolte, R. T.; McDonnell, D. P.; Willson, T. M.; Zuercher, W. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 821.
[554] Meegan, M. J.; Hughes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *J. Med. Chem.* **2001**, *44*, 1072.
[555] Lloyd, D. G.; Smith, H. M.; O'Sullivan, T.; Knox, A. S.; Zisterer, D. M.; Meegan, M. J. *Medicinal Chemistry* **2006**, *2*, 147.
[556] Jan, S.-T.; Rogan, E. G.; Cavalieri, E. L. *Chem. Res. Toxicol.* **1998**, *11*, 408.
[557] Nguyen, A.; Top, S.; Vessiéres, A.; Pigeon, P.; Huché, M.; Hillard, E. A.; Jaouen, G. *J. Organomet. Chem.* **2007**, *692*, 1219.
[558] Nguyen, A.; Top, S.; Pigeon, P.; Vessières, A.; Hillard, E. A.; Plamont, M.-A.; Huché, M.; Rigamonti, C.; Jaouen, G. *Chem.—Eur. J.* **2009**, *15*, 684.
[559] Dobrydneva, Y.; Weatherman, R. V.; Trebley, J. P.; Morrell, M. M.; Fitzgerald, M. C.; Fichandler, C. E.; Chatterjie, N.; Blackmore, P. F. *J. Cardiovasc. Pharmacol.* **2007**, *50*, 380.
[560] Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890.
[561] Letard, J.-F.; Lapouyade, R.; Rettig, W. *Mol. Cryst. Liq. Cryst.* **1993**, *234*, 581.
[562] Asveld, E. W. H.; Kellogg, R. M. *J. Org. Chem.* **1982**, *47*, 1250.
[563] Kim, S.-H.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2000**, *8*, 785.
[564] Imanishi, T.; Ueda, Y.; Minagawa, M.; Hoshino, N.; Miyashita, K. *Tetrahedron Lett.* **1997**, *38*, 3967.
[565] Imanishi, T.; Ueda, Y.; Tainaka, R.; Miyashita, K.; Hoshino, N. *Tetrahedron Lett.* **1997**, *38*, 841.
[566] Miyashita, K.; Minagawa, M.; Ueda, Y.; Tada, Y.; Hoshino, N.; Imanishi, T. *Tetrahedron* **2001**, *57*, 3361.
[567] Chan, K. H.; Leong, W. K.; Jaouen, G.; Leclerq, L.; Top, S.; Vessières, A. *J. Organomet. Chem.* **2006**, *691*, 9.
[568] Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *Synthesis* **2007**, 713.
[569] Top, S.; Kaloun, E. B.; Vessières, A.; Leclercq, G.; Laïos, I.; Ourevitch, M.; Deuschel, C.; McGlinchey, M. J.; Jaouen, G. *ChemBioChem* **2003**, *4*, 754.
[570] Ortin, Y.; Grealis, J.; Scully, C.; Müller-Bunz, H.; Manning, A. R.; McGlinchey, M. J. *J. Organomet. Chem.* **2004**, *689*, 4683.
[571] Gupta, A.; Dwivedy, A.; Keshri, G.; Sharma, R.; Balapure, A. K.; Singh, M. M.; Ray, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6006.
[572] Zekri, O.; Hillard, E. A.; Top, S.; Vessières, A.; Pigeon, P.; Plamont, M.-A.; Huché, M.; Boutamine, S.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 4318.
[573] Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organomet. Chem.* **1997**, *541*, 355.
[574] Jaouen, G.; Top, S.; Vessières, A.; Leclercq, G.; Quivy, J.; Jin, L.; Croisy, A. *C. R. Acad. Sci., Ser. IIc: Chim.* **2000**, *3*, 89.
[575] Heilmann, J. B.; Hillard, E. A.; Plamont, M.-A.; Pigeon, P.; Bolte, M.; Jaouen, G.; Vessiéres, A. *J. Organomet. Chem.* **2008**, *693*, 1716.
[576] Pigeon, P.; Top, S.; Vessières, A.; Huché, M.; Hillard E., A.; Salomon, E.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 2814.
[577] Top, S.; Vessières, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huché, M.; Jaouen, G. *Chem.—Eur. J.* **2003**, *9*, 5223.
[578] Top, S.; Vessières, A.; Cabestaing, C.; Laïos, I.; Leclercq, G.; Provot, C.; Jaouen, G. *J. Organomet. Chem.* **2001**, *637–639*, 500.
[579] Hillard, E. A.; Pigeon, P.; Vessières, A.; Amatore, C.; Jaouen, G. *Dalton Trans.* **2007**, 5073.
[580] Kowalski, K.; Vessières, A.; Top, S.; Jaouen, G.; Zakrzewski, J. *Tetrahedron Lett.* **2003**, *44*, 2749.
[581] Cushman, M.; Golebiewski, W. M.; Pommier, Y.; Mazumder, A.; Reymen, D.; De Clercq, E.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1995**, *38*, 443.

[582] Kim, S.-K.; Park, Y.-I.; Kang, I.-N.; Park, J.-W. *J. Mater. Chem.* **2007**, *17*, 4670.
[583] Casimiro-Garcia, A.; De Clercq, E.; Pannecouque, C.; Witvrouw, M.; Loftus, T. L.; Turpin, J. A.; Buckheit, Jr., R. W.; Fanwick, P. E.; Cushman, M. *Bioorg. Med. Chem.* **2001**, *9*, 2827.
[584] Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2004**, *12*, 5147.
[585] Xu, G. Z.; Micklatcher, M.; Silvestri, M. A.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Buckheit, Jr., R. W.; Cushman, M. *J. Med. Chem.* **2001**, *44*, 4092.
[586] Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Org. Chem.* **2004**, *69*, 7495.
[587] Yan, T.-H.; Paquette, L. A. *Tetrahedron Lett.* **1982**, *23*, 3227.
[588] Karjalainen, A.; Kalapudas, A.; Södervall, M.; Pelkonen, O.; Lammintausta, R. *Eur. J. Pharm. Sci.* **2000**, *11*, 109.
[589] Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275.
[590] Ishiduka, T.; Tsukayama, M.; Kawamura, Y. *Int. J. Mod. Phys. B* **2006**, *20*, 4595.
[591] Casimiro-Garcia, A.; Micklatcher, M.; Turpin, J. A.; Stup, T. L.; Watson, K.; Buckheit, R. W.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 4861.
[592] Caselli, A.; Solari, E.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 8296.
[593] Ruenitz, P. C.; Arrendale, R. F.; Schmidt, W. F.; Thompson, C. B.; Nanavati, N. T. *J. Med. Chem.* **1989**, *32*, 192.
[594] Liu, J.; Murray, E. M.; Young, Jr., V. G., Jr. *Chem. Commun.* **2003**, 1904.
[595] Liu, J.; Suits, E. L.; Boarman, K. J. *Tetrahedron Lett.* **2003**, *44*, 8103.
[596] Schmidt, J. M.; Tremblay, G. B.; Plastina, M. A.; Ma, F.; Bhal, S.; Feher, M.; Dunn-Dufault, R.; Redden, P. R. *Bioorg. Med. Chem.* **2005**, *13*, 1819.
[597] Kannan, A.; De Clercq, E.; Pannecouque, C.; Witvrouw, M.; Hartman, T. L.; Turpin, J. A.; Buckheit, R. W.; Cushman, M. *Tetrahedron* **2001**, *57*, 9385.
[598] Golebiewski, W. M.; Keyes, R. F.; Cushman, M. *Bioorg. Med. Chem.* **1996**, *4*, 1637.
[599] Ruell, J. A.; De Clercq, E.; Pannecouque, C.; Witvrouw, M.; Stup, T. L.; Turpin, J. A.; Buckheit, R. W.; Cushman, M. *J. Org. Chem.* **1999**, *64*, 5858.
[600] Matsumoto, M.; Hiroshima, T.; Chiba, S.; Isobe, R.; Watanabe, N.; Kobayashi, H. *Luminescence* **1999**, *14*, 345.
[601] Watanabe, N.; Kobayashi, H.; Azami, M.; Matsumoto, M. *Tetrahedron* **1999**, *55*, 6831.
[602] Schubert, F.; Knaf, A.; Möller, U.; Cech, D. *Nucleic Acids Res.* **1995**, *23*, 4657.
[603] Bastos, E. L.; Monteiro Leite Ciscato, L. F.; Weiss, D.; Beckert, R.; Baader, W. J. *Synthesis* **2006**, 1781.
[604] Matsumoto, M.; Kawahara, M.; Watanabe, N. *Luminescence* **1999**, *14*, 341.
[605] Gleiter, R.; Krennrich, G.; Bischof, P.; Tsuji, T.; Nishida, S. *Helv. Chim. Acta* **1986**, *69*, 962.
[606] Winkler, J. D.; Sridar, V.; Siegel, M. G. *Tetrahedron Lett.* **1989**, *30*, 4943.
[607] Lima, E. L. D.; Correia, C. R. D. *J Braz. Chem. Soc.* **1997**, *8*, 275.
[608] Brudermüller, M.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 298.
[609] Krause, A.; Musso, H.; Boland, W.; Ahlrichs, R.; Gleiter, R.; Boese, R.; Bär, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1379.
[610] Masson, G.; Lough, A. J.; Manners, I. *Macromolecules* **2008**, *41*, 539.
[611] Shirani, H.; Janosik, T. *J. Org. Chem.* **2007**, *72*, 8984.
[612] Shirani, H.; Bergman, J.; Janosik, T. *Tetrahedron* **2009**, *65*, 8350.
[613] Shirani, H.; Janosik, T. *Organometallics* **2008**, *27*, 3960.
[614] Gies, A.-E.; Pfeffer, M. *J. Org. Chem.* **1999**, *64*, 3650.
[615] Märkl, G.; Sauer, H.; Kreitmeier, P.; Burgemeister, T.; Kastner, F. *Tetrahedron* **1999**, *55*, 13407.
[616] Märkl, G.; Ehrl, R.; Sauer, H.; Kreitmeier, P.; Burgemeister, T. *Helv. Chim. Acta* **1999**, *82*, 59.
[617] Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990.
[618] Mayekar, N. V.; Chattopadhyay, S.; Nayak, S. K. *Lett. Org. Chem.* **2004**, *1*, 203.
[619] Mayekar, N. V.; Chattopadhyay, S.; Nayak, S. K. *Synthesis* **2003**, 2041.
[620] Darabi, H. R.; Jadidi, K.; Mohebbi, A. R.; Faraji, L.; Aghapoor, K.; Shahbazian, S.; Azimzadeh, M.; Nasseri, S. M. *Supramol. Chem.* **2008**, *20*, 327.
[621] Yamato, T.; Fujita, K.; Futatsuki, K.; Tsuzuki, H. *Can. J. Chem.* **2000**, *78*, 1089.

[622] Saisyo, T.; Shiino, M.; Hironaka, T.; Yamato, T. *J. Chem. Res.* **2007**, 141.
[623] Saisyo, T.; Shiino, M.; Shimizu, T.; Paudel, A.; Yamato, T. *J. Chem. Res.* **2008**, 479.
[624] Darabi, H. R.; Mirza-Aghayan, M.; Ali-Saraie, L.; Bolourtchian, M.; Neumüller, B.; Ghassemzadeh, M. *Supramol. Chem.* **2003**, *15*, 55.
[625] Mamane, V.; Fort, Y. *J. Org. Chem.* **2005**, *70*, 8220.
[626] Tirado-Rives, J.; Oliver, M. A.; Fronczek, F. R.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 1627.
[627] Wang, Z.; Zhu, S.; Shi, J.; Wang, H. *Beilstein J. Org. Chem.* **2009**, *5*, No. 55.
[628] Tirado-Rives, J.; Gandour, R. D.; Fronczek, F. R. *Tetrahedron Lett.* **1982**, *23*, 1639.
[629] Grützmacher, H.-F.; Neumann, E. *Chem. Ber.* **1993**, *126*, 1495.
[630] Kuroda, S.; Yazaki, J.-i.; Maeda, S.; Yamazaki, K.; Yamada, M.; Shimao, I.; Yasunami, M. *Tetrahedron Lett.* **1992**, *33*, 2825.
[631] Macomber, R. S.; Rardon, D. E.; Emge, T. J. *J. Org. Chem.* **1992**, *57*, 433.
[632] Mateo, C.; Pérez-Melero, C.; Peláez, R.; Medarde, M. *J. Org. Chem.* **2005**, *70*, 6544.
[633] Merz, A.; Karl, A.; Futterer, T.; Stacherdinger, N.; Schneider, O.; Lex, J.; Luboch, E.; Biernat, J. F. *Liebigs Ann. Chem.* **1994**, 1199.
[634] Marshall, J. A.; Chung, K.-H. *J. Org. Chem.* **1979**, *44*, 1566.
[635] Mirza-Aghayan, M.; Darabi, H. R.; Ali-Saraie, L.; Ghassemzadeh, M.; Bolourtchian, M.; Jalali-Heravi, M.; Neumüller, B. *Z Anorg. Allg. Chem.* **2002**, *628*, 681.
[636] Ravishankar, T.; Chinnakali, K.; Rajakumar, P.; Murali, V.; Usman, A.; Fun, H.-K. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2003**, *59*, O290.
[637] Ben, I.; Castedo, L.; Saá, J. M.; Seijas, J. A.; Suau, R.; Tojo, G. *J. Org. Chem.* **1985**, *50*, 2236.
[638] Rajakumar, P.; Murali, V. *Tetrahedron* **2004**, *60*, 2351.
[639] Dubois, F.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 5039.
[640] Srinivasan, M.; Sankararaman, S.; Dix, I.; Jones, P. G. *Org. Lett.* **2000**, *2*, 3849.
[641] Castedo, L.; Saá, J. M.; Suau, R.; Tojo, G. *Tetrahedron Lett.* **1983**, *24*, 5419.
[642] Yamato, T.; Fujita, K.; Okuyama, K.; Tsuzuki, H. *New J. Chem.* **2000**, *24*, 221.
[643] Tanner, D.; Wennerström, O.; Norinder, U.; Müllen, K.; Trinks, R. *Tetrahedron* **1986**, *42*, 4499.
[644] Meier, H.; Fetten, M. *Tetrahedron Lett.* **2000**, *41*, 1535.
[645] Tanaka, K.; Suzuki, H.; Osuga, H. *Tetrahedron Lett.* **1997**, *38*, 457.
[646] Shimizu, I.; Umezawa, H.; Kanno, T.; Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2023.
[647] Rajakumar, P.; Gayatri Swaroop, M.; Jayavelu, S.; Murugesan, K. *Tetrahedron* **2006**, *62*, 12041.
[648] Rajakumar, P.; Gayatri Swaroop, M. *Tetrahedron Lett.* **2004**, *45*, 6165.
[649] Müllen, K.; Unterberg, H.; Huber, W.; Wennerström, O.; Norinder, U.; Tanner, D.; Thulin, B. *J. Am. Chem. Soc.* **1984**, *106*, 7514.
[650] Yamato, T.; Hironaka, T.; Saisyo, T.; Manabe, T.; Okuyama, K. *J. Chem. Res. (S)* **2003**, 63.
[651] Kasahara, A.; Izumi, T.; Shimizu, I.; Satou, M.; Katou, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2434.
[652] Saisyo, T.; Shiino, M.; Hu, J.–Y.; Yamato, T. *J. Chem. Res.* **2007**, 621.
[653] Speicher, A.; Kolz, J.; Sambanje, R. P. *Synthesis* **2002**, 2503.
[654] Yamamoto, K. *Pure Appl. Chem.* **1993**, *65*, 157.
[655] Kasahara, A.; Izumi, T.; Shimizu, I.; Oikawa, T.; Umezawa, H.; Hoshino, I. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1143.
[656] Kasahara, A.; Izumi, T.; Shimizu, I. *Chem. Lett.* **1979**, 1119.
[657] Esser, B.; Rominger, F.; Gleiter, R. *J. Am. Chem. Soc.* **2008**, *130*, 6716.
[658] Yamato, T.; Fujita, K.; Abe, T.; Tsuzuki, H. *New J. Chem.* **2001**, *25*, 728.
[659] Marshall, J. A.; Black, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 7581.
[660] Aukauloo, M. A.; Guilard, R. *New J. Chem.* **1994**, *18*, 1205.
[661] Sessler, J. L.; Brucker, E. A.; Weghorn, S. J.; Kisters, M.; Schäfer, M.; Lex, J.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2308.
[662] Kozaki, M.; Parakka, J. P.; Cava, M. P. *J. Org. Chem.* **1996**, *61*, 3657.
[663] Vogel, E.; Binsack, B.; Hellwig, Y.; Erben, C.; Heger, A.; Lex, J.; Wu, Y.-D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2612.
[664] Eguchi, T.; Terachi, T.; Kakinuma, K. *Tetrahedron Lett.* **1993**, *34*, 2175.

[665] Lin, H.-C.; Lin, W.-Y.; Bai, H.-T.; Chen, J.-H.; Jin, B.-Y.; Luh, T.-Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 897.
[666] Rajakumar, P.; Gayatri Swaroop, M. *Tetrahedron Lett.* **2005**, *46*, 8543.
[667] Suzuki, T.; Tanaka, S.; Higuchi, H.; Kawai, H.; Fujiwara, K. *Tetrahedron Lett.* **2004**, *45*, 8563.
[668] Eguchi, T.; Terachi, T.; Kakinuma, K. *J. Chem. Soc., Chem. Commun.* **1994**, 137.
[669] Eguchi, T.; Arakawa, K.; Terachi, T.; Kakinuma, K. *J. Org. Chem.* **1997**, *62*, 1924.
[670] Arakawa, K.; Eguchi, T.; Kakinuma, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2419.
[671] Merner, B. L.; Dawe, L. N.; Bodwell, G. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5487.
[672] Lhoták, P.; Zieba, R.; Hromádko, V.; Stibor, I.; Sykora, J. *Tetrahedron Lett.* **2003**, *44*, 4519.
[673] Rojanathanes, R.; Pipoosananakaton, B.; Tuntulani, T.; Bhanthumnavin, W.; Orton, J. B.; Cole, S. J.; Hursthouse, M. B.; Grossel, M. C.; Sukwattanasinitt, M. *Tetrahedron* **2005**, *61*, 1317.
[674] Sukwattanasinitt, M.; Rojanathanes, R.; Tuntulani, T.; Sritana-Anant, Y.; Ruangpornvisuti, V. *Tetrahedron Lett.* **2001**, *42*, 5291.
[675] Eguchi, T.; Kano, H.; Kakinuma, K. *Chem. Commun.* **1996**, 365.
[676] Vogel, E.; Bröring, M.; Weghorn, S. J.; Scholz, P.; Deponte, R.; Lex, J.; Schmickler, H.; Schaffner, K.; Braslavsky, S. E.; Müller, M.; Pörting, S.; Fowler, C. J.; Sessler, J. L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1651.
[677] Eguchi, T.; Ibaragi, K.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 2689.
[678] Okarma, P. J.; Caringi, J. J. *Org. Prep. Proced. Int.* **1985**, *17*, 212.
[679] Clive, D. L. J.; Murthy, K. S. K.; Zhang, C.; Hayward, W. D.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1990**, 509.
[680] Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* **1985**, *26*, 1981.
[681] Nakayama, J.; Ikuina, Y.; Murai, F.; Hoshino, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1072.
[682] Paquette, L. A.; Dressel, J.; Pansegrau, P. D. *Tetrahedron Lett.* **1987**, *28*, 4965.
[683] Pauw, J. E.; Weedon, A. C. *Tetrahedron Lett.* **1982**, *23*, 5485.
[684] Dang, Y.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 6901.
[685] Dang, Y.; Chen, Y. *Eur. J. Org. Chem.* **2007**, 5661.
[686] Disanayaka, B. W.; Weedon, A. C. *J. Chem. Soc., Chem. Commun.* **1985**, 1282.
[687] Chen, Y.; Zeng, D. X.; Fan, M. G. *Org. Lett.* **2003**, *5*, 1435.
[688] Huang, Z.-N.; Xu, B.-A.; Jin, S.; Fan, M.-G. *Synthesis* **1998**, 1092.
[689] Venkataiah, B.; Ramesh, C.; Ravindranath, N.; Das, B. *Phytochemistry* **2003**, *63*, 383.
[690] Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *ARKIVOC* **2003**, 188.
[691] Lucas, L. N.; de Jong, J. J. D.; van Esch, J. H.; Kellogg, R. M.; Feringa, B. L. *Eur. J. Org. Chem.* **2003**, 155.
[692] Lucas, L. N.; van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 2313.
[693] Lucas, L. N.; van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 1775.
[694] Baumstark, A. L.; Bechara, E. J. H.; Semigran, M. J. *Tetrahedron Lett.* **1976**, 3265.
[695] Paquette, L. A.; Gardlik, J. M.; McCullough, K. J.; Hanzawa, Y. *J. Am. Chem. Soc.* **1983**, *105*, 7644.
[696] Han, Y.; Zhang, Z. B.; Xiao, J. P.; Yan, W. P.; Fan, M. G. *Chin. Chem. Lett.* **2005**, *16*, 175.
[697] Zeng, D. X.; Chen, Y. *Synlett* **2006**, 490.
[698] Marshall, J. A.; Constantino, M.; Black, T. H. *Synth. Commun.* **1980**, *10*, 689.
[699] McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Van Duyne, G.; Gleiter, R.; Schäfer, W.; White, D. H. *J. Am. Chem. Soc.* **1984**, *106*, 5018.
[700] Vogel, E.; Neumann, B.; Klug, W.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1046.
[701] Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1994**, *37*, 3878.
[702] Yamato, T.; Fujita, K.; Tsuzuki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2089.
[703] Yamato, T.; Miyamoto, S.; Hironaka, T.; Miura, Y. *Org. Lett.* **2005**, *7*, 3.
[704] Rathore, R.; Weigand, U.; Kochi, J. K. *J. Org. Chem.* **1996**, *61*, 5246.
[705] Jenny, L.; Borschberg, H.-J. *Helv. Chim. Acta* **1995**, *78*, 715.
[706] Krayushkin, M. M.; Yarovenko, V. N.; Semenov, S. L.; Zavarzin, I. V.; Martynkin, A. Y.; Uzhinov, B. M. *Russ. J. Org. Chem.* **2003**, *39*, 1656.

[707] Yamato, T.; Saisyo, T.; Hironaka, T.; Miyamoto, S. *J. Chem. Res.* **2006**, 558.
[708] Reitz, D. B.; Huang, H.-C.; Li, J. J.; Garland, D. J.; Manning, R. E.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 867.
[709] Rybalkin, V. P.; Shepelenko, E. N.; Popova, L. L.; Dubonosov, A. D.; Metelitsa, A. V.; Makarova, N. I.; Bren, V. A.; Minkin, V. I. *Russ. J. Org. Chem.* **2006**, *42*, 619.
[710] Huang, Z.; Yang, Q.-Z.; Kucharski, T. J.; Khvostichenko, D.; Wakeman, S. M.; Boulatov, R. *Chem.—Eur. J.* **2009**, *15*, 5212.
[711] Shepelenko, E. N.; Rybalkin, V. P.; Karamov, O. G.; Makarova, N. I.; Metelitsa, A. V.; Popova, L. L.; Bren, V. A. *Russ. J. Org. Chem.* **2006**, *42*, 1727.
[712] Hu, J.; Jiang, X.; He, T.; Zhou, J.; Hu, Y. F.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1820.
[713] Krayushkin, M. M.; Migulin, V. A.; Yarovenko, V. N.; Barachevskii, V. A.; Vorontsova, L. G.; Starikova, Z. A.; Zavarzin, I. V.; Bulgakova, V. N. *Mendeleev Commun.* **2007**, *17*, 125.
[714] Huang, Z. N.; Jin, S.; Fan, M. G. *Chin. Chem. Lett.* **1997**, *8*, 7.
[715] Walko, M.; Feringa, B. L. *Chem. Commun.* **2007**, 1745.
[716] Rajca, A.; Pink, M.; Xiao, S.; Miyasaka, M.; Rajca, S.; Das, K.; Plessel, K. *J. Org. Chem.* **2009**, *74*, 7504.
[717] Knapp, K. M.; Goldfuss, B.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 5259.
[718] Huang, Z.; Yang, Q.-Z.; Khvostichenko, D.; Kucharski, T. J.; Chen, J.; Boulatov, R. *J. Am. Chem. Soc.* **2009**, *131*, 1407.
[719] Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926.
[720] Yamato, T.; Hironaka, T.; Shiino, M.; Saisyo, T.; Miyamoto, S. *J. Chem. Res.* **2006**, 110.
[721] Yamato, T.; Hironaka, T.; Miyamoto, S. *J. Chem. Res.* **2006**, 393.
[722] Kuroda, S.; Obata, Y.; Thanh, N. C.; Miyatake, R.; Horino, Y.; Oda, M. *Tetrahedron Lett.* **2008**, *49*, 552.
[723] Lee, W. Y.; Park, C. H. *J. Org. Chem.* **1993**, *58*, 7149.
[724] Lee, W. Y.; Park, C. H.; Kim, H.-J.; Kim, S. *J. Org. Chem.* **1994**, *59*, 878.
[725] Emond, S. J.; Debroy, P.; Rathore, R. *Org. Lett.* **2008**, *10*, 389.
[726] Komatsu, K.; Murata, M.; Murata, Y. *Science* **2005**, *307*, 238.
[727] Komatsu, K.; Murata, Y. *Chem. Lett.* **2005**, *34*, 886.
[728] Murata, M.; Murata, Y.; Komatsu, K. *J. Am. Chem. Soc.* **2006**, *128*, 8024.
[729] Komatsu, K. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2285.
[730] Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373.
[731] Raubo, P.; Kulagowski, J. J.; Chicchi, G. G. *Synlett* **2006**, 271.
[732] Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1997**, *38*, 2397.
[733] Saunders, M.; Krause, N. *J. Am. Chem. Soc.* **1990**, *112*, 1791.
[734] McMurry, J. E.; Hodge, C. N. *J. Am. Chem. Soc.* **1984**, *106*, 6450.
[735] McMurry, J. E.; Lectka, T.; Hodge, C. N. *J. Am. Chem. Soc.* **1989**, *111*, 8867.
[736] Rank, E.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1045.
[737] Eckhardt, M.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1093.
[738] Trehan, I. R.; Kad, G. L.; Seth, V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1991**, *30*, 793.
[739] Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.
[740] Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607.
[741] Nickon, A.; Hrnjez, B. *Tetrahedron* **1988**, *44*, 1905.
[742] Ferri, F.; Brückner, R. *Liebigs Ann./Recl.* **1997**, 961.
[742a] Rucker, M.; Brückner, R. *Tetrahedron Lett.* **1997**, *38*, 7353.
[743] Yue, X.; Li, Y. *Bull. Soc. Chim. Belg.* **1995**, *104*, 69.
[744] Jing, L.; Jiong, L.; Zuosheng, L.; Ying, L.; Yulin, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2851.
[745] Lan, J.; Liu, Z.; Cen, W.; Xing, Y.; Li, Y. *Tetrahedron Lett.* **1999**, *40*, 1963.
[746] Li, Y.; Li, W.; Li, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2953.
[747] Liu, Z.; Li, W. Z.; Peng, L.; Li, Y.; Li, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4250.
[748] Hinkley, S. F. R.; Perry, N. B.; Weavers, R. T. *Tetrahedron* **2005**, *61*, 3671.

[749] Clive, D. L. J.; Murthy, K. S. K.; George, R.; Poznansky, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2099.
[750] Gao, F.; Burnell, D. J. *Tetrahedron Lett.* **2007**, *48*, 8185.
[751] Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329.
[752] Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773.
[753] Matsumoto, M.; Watanabe, N.; Kasuga, N. C.; Hamada, F.; Tadokoro, K. *Tetrahedron Lett.* **1997**, *38*, 2863.
[754] Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.
[755] Ding, F.; Zhang, Y.; Qu, B.; Li, G.; Farina, V.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1067.
[756] Li, W.; Li, Y.; Li, Y. *Bull. Soc. Chim. Belg.* **1993**, *102*, 503.
[757] Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1990**, 150.
[758] Fan, X.; Zhang, X. *J. Chem. Res. (S)* **2003**, 696.
[758a] Fan, X.; Zhang, Y. *Tetrahedron* **2003**, *59*, 1917.
[759] Watanabe, N.; Nagashima, Y.; Yamazaki, T.; Matsumoto, M. *Tetrahedron* **2003**, *59*, 4811.
[760] Ogawa, A.; Nanke, T.; Takami, N.; Ryu, I.; Kambe, N.; Sonoda, N. *Kidorui* **1994**, *24*, 212.
[761] Cozzi, P. G.; Prati, G. P.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1997**, *127*, 403.
[762] Li, W.; Li, Y.; Li, Y. *Chem. Lett.* **1994**, 741.
[763] Hu, W. H.; Guo, Z. R.; Bai, A. P.; Xu, Z. B. *Chin. Chem. Lett.* **2002**, *13*, 296.
[764] Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Li, J. *Bioorg. Med. Chem.* **2003**, *11*, 1153.
[765] Hu, W.; Guo, Z.; Yi, X.; Guo, C.; Chu, F.; Cheng, G. *Bioorg. Med. Chem.* **2003**, *11*, 5539.
[766] Fürstner, A.; Ptock, A.; Weintritt, H.; Goddard, R.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 678.
[767] Yang, W.; He, H.; Drueckhammer, D. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1714.
[768] Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620.
[769] Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087.
[770] Vogel, E.; Jux, N.; Rodriguez-Val, E.; Lex, J.; Schmickler, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1387.
[771] Nußbaumer, T.; Krieger, C.; Neidlein, R. *Eur. J. Org. Chem.* **2000**, 2449.
[772] Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 411.
[773] Vogel, E.; Köcher, M.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 257.
[774] Munno, G. D.; Lucchesini, F.; Neidlein, R. *Tetrahedron* **1993**, *49*, 6863.
[775] Ellinger, F.; Gieren, A.; Hübner, T.; Lex, J.; Lucchesini, F.; Merz, A.; Neidlein, R.; Salbeck, J. *Monatsh. Chem.* **1993**, *124*, 931.
[776] Dahlmann, U.; Krieger, C.; Neidlein, R. *Eur. J. Org. Chem.* **1998**, 525.
[777] Hu, Z.; Cava, M. P. *Tetrahedron Lett.* **1994**, *35*, 3493.
[778] Michels, H.-P.; Nieger, M.; Vögtle, F. *Chem. Ber.* **1994**, *127*, 1167.
[779] Zimmermann, K.; Haenel, M. W. *Synlett* **1997**, 609.
[780] Märkl, G.; Ehrl, R.; Kreitmeier, P.; Burgemeister, T. *Helv. Chim. Acta* **1998**, *81*, 93.
[781] Märkl, G.; Sauer, H.; Kreitmeier, P.; Burgemeister, T.; Kastner, F.; Adolin, G.; Nöth, H.; Polborn, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1151.
[782] Vogel, E.; Balci, M.; Pramod, K.; Koch, P.; Lex, J.; Ermer, O. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 928.
[783] Vogel, E.; Köcher, M.; Lex, J.; Ermer, O. *Isr. J. Chem.* **1989**, *29*, 257.
[784] Kawase, T.; Darabi, H. R.; Uchimiya, R.; Oda, M. *Chem. Lett.* **1995**, 499.
[785] Song, Y.; Di, C.; Yang, X.; Li, S.; Xu, W.; Liu, Y.; Yang, L.; Shuai, Z.; Zhang, D.; Zhu, D. *J. Am. Chem. Soc.* **2006**, *128*, 15940.
[786] Song, Y.; Di, C.-a.; Xu, W.; Liu, Y.; Zhang, D.; Zhu, D. *J. Mater. Chem.* **2007**, *17*, 4483.
[787] Märkl, G.; Knott, T.; Kreitmeier, P.; Burgemeister, T.; Kastner, F. *Tetrahedron* **1996**, *52*, 11763.
[787a] Märkl, G.; Knott, T.; Kreitmeier, P.; Burgemeister, T.; Kastner, F. *Helv. Chim. Acta* **1998**, *81*, 1480.
[787b] Märkl, G.; Knott, T.; Kreitmeier, P.; Burgemeister, T.; Kastner, F. *Helv. Chim. Acta* **2000**, *83*, 592.

[788] Sargent, A. L.; Hawkins, I. C.; Allen, W. E.; Liu, H.; Sessler, J. L.; Fowler, C. J. *Chem.—Eur. J.* **2003**, *9*, 3065.
[789] Memminger, K.; Oeser, T.; Müller, T. J. J. *Org. Lett.* **2008**, *10*, 2797.
[790] Rajakumar, P.; Kanagalatha, R. *Tetrahedron Lett.* **2007**, *48*, 8496.
[791] Hu, Z.; Scordilis-Kelley, C.; Cava, M. P. *Tetrahedron Lett.* **1993**, *34*, 1879.
[792] Märkl, G.; Stiegler, J.; Kreitmeier, P.; Burgemeister, T.; Kastner, F.; Dove, S. *Helv. Chim. Acta* **1997**, *80*, 14.
[793] Matsumoto, K.; Minami, H.; Kawase, T.; Oda, M. *Org. Biomol. Chem.* **2004**, *2*, 2323.
[794] Darabi, H. R.; Kawase, T.; Oda, M. *Tetrahedron Lett.* **1995**, *36*, 9525.
[795] Kawase, T.; Ueda, N.; Darabi, H. R.; Oda, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1556.
[796] Kawase, T.; Hosokawa, Y.; Kurata, H.; Oda, M. *Chem. Lett.* **1999**, 745.
[797] Guilard, R.; Aukauloo, M. A.; Tardieux, C.; Vogel, E. *Synthesis* **1995**, 1480.
[798] Vogel, E.; Koch, P.; Hou, X.-L.; Lex, J.; Lausmann, M.; Kisters, M.; Aukauloo, M. A.; Richard, P.; Guilard, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1600.
[799] Nussbaumer, T.; Neidlein, R. *Helv. Chim. Acta* **2000**, *83*, 1161.
[800] Kurata, H.; Haruki, K.; Nakaminami, H.; Kawase, T.; Oda, M. *Chem. Lett.* **2003**, *32*, 422.
[801] Kurata, H.; Nakaminami, H.; Matsumoto, K.; Kawase, T.; Oda, M. *Chem. Commun.* **2001**, 529.
[802] Märkl, G.; Bruns, D.; Dietl, H.; Kreitmeier, P. *Helv. Chim. Acta* **2001**, *84*, 2220.
[803] Jux, N.; Koch, P.; Schmickler, H.; Lex, J.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1385.
[804] Johnson, M. R.; Miller, D. C.; Bush, K.; Becker, J. J.; Ibers, J. A. *J. Org. Chem.* **1992**, *57*, 4414.
[805] Kawase, T.; Nakamura, T.; Utsumi, K.; Matsumoto, K.; Kurata, H.; Oda, M. *Chem. Asian J.* **2008**, *3*, 573.
[806] Mártire, D. O.; Jux, N.; Aramendía, P. F.; Negri, R. M.; Lex, J.; Braslavsky, S. E.; Schaffner, K.; Vogel, E. *J. Am. Chem. Soc.* **1992**, *114*, 9969.
[807] Sawada, T.; Morita, M.; Chifuku, K.; Kuwahara, Y.; Shosenji, H.; Takafuji, M.; Ihara, H. *Tetrahedron Lett.* **2007**, *48*, 9051.
[808] Paek, K.-S.; Cram, D. J. *Bull. Korean Chem. Soc.* **1989**, *10*, 568.
[809] Sánchez-García, D.; Borrell, J. I.; Nonell, S. *Org. Lett.* **2009**, *11*, 77.
[810] Stępień, M.; Donnio, B.; Sessler, J. L. *Chem.—Eur. J.* **2007**, *13*, 6853.
[811] Kawase, T.; Daifuku, Y.; Hirao, Y.; Matsumoto, K.; Kurata, H.; Kubo, T. *C. R. Hebd. Sceances Acad. Sci., Ser. IIc*, **2009**, *12*, 403.
[812] Nonell, S.; Borrell, J. I.; Borrós, S.; Colominas, C.; Rey, O.; Rubio, N.; Sánchez-García, D.; Teixidó, J. *Eur. J. Org. Chem.* **2003**, 1635.
[813] Paek, K.-S.; Cram, D. J. *Bull. Korean Chem. Soc.* **1989**, *10*, 572.
[814] Kurata, H.; Haruki, K.; Oda, M. *Chem. Lett.* **2005**, *34*, 484.
[815] Piwoński, H.; Hartschuh, A.; Urbańska, N.; Pietraszkiewicz, M.; Sepiol, J.; Meixner, A. J.; Waluk, J. *J. Phys. Chem. C* **2009**, *113*, 11514.
[816] Nakao, K.; Nishimura, M.; Tamachi, T.; Kuwatani, Y.; Miyasaka, H.; Nishinaga, T.; Iyoda, M. *J. Am. Chem. Soc.* **2006**, *128*, 16740.
[817] Liu, W.-J.; Zhou, Y.; Zhou, Q.-F.; Ma, Y.; Pei, J. *Org. Lett.* **2008**, *10*, 2123.
[818] Miller, D. C.; Johnson, M. R.; Ibers, J. A. *J. Org. Chem.* **1994**, *59*, 2877.
[819] Miller, D. C.; Johnson, M. R.; Becker, J. J.; Ibers, J. A. *J. Heterocycl. Chem.* **1993**, *30*, 1485.

CHAPTER 2

CATALYTIC ASYMMETRIC KETENE [2 + 2] AND [4 + 2] CYCLOADDITIONS

SCOTT G. NELSON AND ROBERT D. DURA

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

TIMOTHY J. PEELEN

Department of Chemistry, Lebanon Valley College, Annville, Pennsylvania 17003

CONTENTS

	PAGE
INTRODUCTION	474
MECHANISM AND STEREOCHEMISTRY	476
Molecular Orbital Interactions	476
Thermal Cycloadditions	477
Electronic Structure of Ketenes	477
Modes of Catalysis	477
Lewis Acid Catalysis	477
Lewis Base Catalysis	478
Insights from Diastereoselective Ketene–Carbonyl Cycloadditions	479
Ketene–Imine Cycloadditions	480
[4 + 2] Cycloadditions Involving Ketenes as Dienes or Dienophiles	482
SCOPE AND LIMITATIONS	484
Lewis Base Catalyzed [2 + 2] Ketene–Carbonyl Cycloadditions	484
Cinchona Alkaloid Catalysis with Activated Aldehydes and Ketones	484
Alkaloid-Catalyzed [2 + 2] Cycloadditions of Unactivated Aldehydes	487
Fe(II)–Azaindene Catalysts for Ketene–Aldehyde Cycloadditions	492
Heterocyclic Carbene Catalysis with Trifluoromethyl Ketones	493
Intramolecular Ketene–Aldehyde [2 + 2] Cycloadditions	493
Catalytic Asymmetric Ketene Dimerization	494
Cinchona Alkaloid Catalysts	494
1,2,4-Triazolium Carbene Catalysts	496
Phosphine Catalysts	496
Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloadditions	497
Al(III)-Catalyzed Reactions Involving Pregenerated Ketenes	497

sgnelson@pitt.edu

Organic Reactions, Vol. 82, Edited by Scott E. Denmark et al.

© 2013 Organic Reactions, Inc. Published 2013 by John Wiley & Sons, Inc.

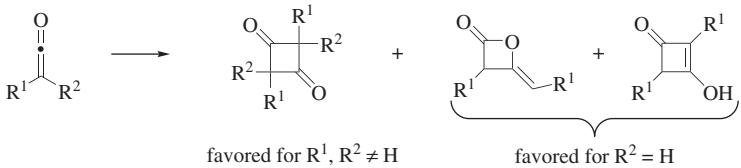
Al(III)-Catalyzed Reactions Involving Trimethylsilylketene 498
Ti(IV)-Catalyzed Reactions Involving Trialkylsilylketenes 500
Cu(II)-Catalyzed Reactions Involving Trimethylsilylketene 500
Al(III)-Catalyzed Acyl Halide–Aldehyde Cyclocondensations 502
Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloadditions 507
Cinchona Alkaloid Catalysts 507
Fe(II)–Azaindene Catalysts 510
Heterocyclic Carbene Catalysts 512
[4 + 2] Cycloadditions: Ketene Dienophiles 513
o-Benzoquinone and *o*-Benzoquinone Imine Dienes 513
Thiocarbamoyl Imine-Derived Dienes 516
Conjugated Enone Dienes 518
[4 + 2] Cycloadditions: Ketene Dienes 519
APPLICATIONS TO SYNTHESIS 520
Lewis Base and Lewis Acid Catalyzed [2 + 2] Ketene–Aldehyde Cycloadditions 521
Al(III)-Catalyzed Reactions Involving Trimethylsilylketene 521
Alkaloid-Catalyzed [2 + 2] Cycloadditions of Unactivated Aldehydes . . . 522
Cinchona Alkaloid-Catalyzed Ketene Dimerization 523
Al(III)-Catalyzed Acyl Halide–Aldehyde Cyclocondensations 524
Alkaloid-Catalyzed [2 + 2] Ketene–Imine Cycloadditions 525
COMPARISON WITH OTHER METHODS 526
Diastereoselective [2 + 2] Cycloadditions 527
Ketene–Imine Cycloadditions 527
Ketene–Aldehyde Cycloadditions 530
[2 + 2] Cycloadducts from Enolate Addition Reactions 531
Reaction Design 531
Mannich-Based Approaches to β-Lactams 532
Aldol-Based Approaches to β-Lactones 537
β-Lactams from Nitrone–Alkyne Cycloadditions 538
Alternative Approaches to [4 + 2] Cycloadducts 541
Hetero-Diels–Alder Reactions 542
Catalytic Asymmetric Allylation-Lactonization 545
EXPERIMENTAL CONDITIONS 546
EXPERIMENTAL PROCEDURES 548
(*R*)-4-Trichloromethyl-2-oxetanone [Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition of an Activated Aldehyde Catalyzed by a *Cinchona* Alkaloid] . 548
(*R*)-4-(1,1-Dichloroheptyl)-2-oxetanone [*Cinchona* Alkaloid-Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition with Ketene Generated by Amine-Mediated Dehydrohalogenation of Acetyl Chloride] 548
(3*R*,4*S*)-3-Methyl-4-(2-phenylethyl)oxetan-2-one [Lewis Acid Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition] 549
(*S*)-3,3-Diethyl-4-phenyloxetan-2-one [Fe(II)-Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition] 550
(3*S*,4*S*)-3-Ethyl-3,4-diphenyl-4-(trifluoromethyl)oxetan-2-one [Heterocyclic Carbene-Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition of a Trifluoromethyl Ketone] 550
(1*R*,2*S*)-6-Oxabicyclo[3.2.0]heptan-7-one [Intramolecular Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition] 551
(*R*)-1-Hydroxy-2-methyl-3-pentanone [Catalytic Asymmetric Ketene Dimerization–$LiAlH_4$ Reduction] 551
(*S*,*Z*)-3-Ethyl-3-phenyl-4-(1-phenylpropylidene)oxetan-2-one [Heterocyclic Carbene-Catalyzed Asymmetric Dimerization of an Alkyl Aryl Ketene] . . 552

tert-Butyl (*R*,2*E*,4*E*)-3,5,7-Trimethyl-11-[(2*R*,3*S*)-4-oxo-3-(trimethylsilyl) oxetan-2-yl]undeca-2,4-dienoate (**129**) and *tert*-Butyl (*R*,2*E*,4*E*)-3,5,7-Trimethyl-11-[(2*S*,3*R*)-4-oxo-3-(trimethylsilyl)oxetan-2-yl]undeca-2,4-dienoate (**130**) [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Amine Complex; AAC Reaction] 553
4-Cyclohexyloxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of the Ti(IV)–TADDOL Complex] . . . 554
(2*S*)-4-Oxo-oxetane-2-carboxylic Acid Ethyl Ester [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of Cu(II)–Bis(oxazoline) Complex] 555
(*S*)-4-(9-Decylenyl)oxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Bis(sulfonamide) Complex] . . 555
(3*R*,4*R*)-3-Methyl-4-(2-phenylethyl)oxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Salen Complex] 556
Ethyl (2*R*,3*R*)-4-Oxo-3-phenyl-1-tosylazetidine-2-carboxylate [Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloaddition in the Presence of a *Cinchona* Alkaloid Catalyst] 557
1-Ethyl 4-Methyl (2*R*,3*R*)-2-Benzamido-3-phenylsuccinate [Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloaddition–Solvolysis] 557
(*S*)-3-Phenyl-2-tosyl-2-azaspiro[3,6]decane-1-one [Fe(II)–Azaindene-Catalyzed [2 + 2] Ketene–Imine Cycloaddition] 558
(3*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-3-ethyl-4-(4-chlorophenyl)-3-phenylazetidin-2-one [Heterocyclic Carbene-Catalyzed [2 + 2] Ketene–Imine Cycloaddition] . . 559
(*R*)-5,6,7,8-Tetrachloro-3-ethylbenzo[*b*][1,4]dioxin-2(3*H*)-one [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene–Benzoquinone Cycloaddition] . . . 559
Methyl (*R*)-2-(*N*-(4,5-Dichloro-2-hydroxyphenyl)-4-nitrobenzamido)-3-(1,3-dioxoisoindolin-2-yl)propanoate [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene–Quinone Imine Cycloaddition] 560
(4*S*,5*R*)-2-(Ethylthio)-5-methyl-4-(2-phenylethyl)-4,5-dihydro-1,3-thiazin-6-one [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene Thiocarbonyl Imine Cycloaddition] 561
Ethyl (3*R*,4*R*)-3,4-Dihydro-3-ethyl-2-oxo-3,6-diphenyl-2*H*-pyran-4-carboxylate [Heterocyclic Carbene-Catalyzed Ketene [4 + 2] Cycloaddition with an Enone] 562
(*R*)-4-Isopropyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one [Lewis Base Catalyzed Alkenyl Ketene [4 + 2] Cycloaddition] 562
TABULAR SURVEY 563
Chart 1. Catalysts and Catalyst Precursors Used in Tables 565
Table 1. *Cinchona* Alkaloid-Catalyzed Cycloadditions to Activated Carbonyl Compounds 568
Table 2A. *Cinchona* Alkaloid-Catalyzed Cycloadditions to Unactivated Aldehydes 570
Table 2B. *Cinchona* Alkaloid-Catalyzed Cycloadditions to Enantioenriched Aldehydes 573
Table 3. Fe(II)–Azaindene-Catalyzed Cycloadditions to Aldehydes . . . 577
Table 4. Triazolium Carbene-Catalyzed Cycloadditions to Trifluoromethyl Ketones 579
Table 5A. *Cinchona* Alkaloid-Catalyzed Dimerization of Monosubstituted Ketenes 581
Table 5B. Lewis Base Catalyzed Dimerization of Disubstituted Ketenes . . 583
Table 6A. Lewis Acid Catalyzed Cycloadditions of Pregenerated Ketenes to Aldehydes 585
Table 6B. Lewis Acid Catalyzed Cycloadditions of Trialkylsilylketenes to Carbonyl Compounds 586

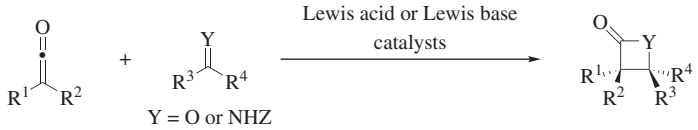
Table 7. Al(III)-Catalyzed Cycloadditions of In Situ Generated Ketenes to Aldehydes 591
Table 8A. *Cinchona* Alkaloid-Catalyzed Cycloadditions to Imines 597
Table 8B. Fe(II)–4-Azaindene-Catalyzed Cycloadditions of Disubstituted Ketenes to Imines 602
Table 8C. Heterocyclic Carbene-Catalyzed Cycloadditions to Imines 604
Table 9. [4 + 2] Cycloadditions to *o*-Benzoquinone and *o*-Benzoquinone Imine Dienes 608
Table 10. [4 + 2] Cycloadditions to Thioacyl Imines 611
Table 11. [4 + 2] Cycloadditions of Vinyl Ketenes 612
Table 12. [4 + 2] Cycloadditions to Enones 614
REFERENCES 616

INTRODUCTION

Among the defining characteristics of organic cumulenes is their propensity to undergo thermal [2 + 2] cycloadditions despite the formally "forbidden" nature of these reactions.[1,2] Ketenes are among the cumulenes that are particularly reactive partners for [2 + 2] cycloaddition reactions.[3] For example, ketenes dimerize under ambient conditions to generate cyclobutane-1,3-dione, cyclobutenone, or β-lactone structures depending on the C2 ketene substituents (Scheme 1);[4,5] ketene itself rapidly dimerizes to generate diketene (4-methylideneoxetan-2-one), a shelf-stable, commercially available precursor to ketene.[6] Both Lewis acid and Lewis base catalysts are effective in diverting ketene reactivity away from dimerization processes to enable efficient intermolecular [2 + 2] cycloadditions with electrophilic ketenophiles. As both Lewis acidic and Lewis basic catalysts for the ketene-dependent [2 + 2] cycloadditions are involved in the stereochemistry-defining step, enantioenriched variants of these catalysts have been effective in developing highly enantioselective cycloadditions involving carbonyl- and imine-derived ketenophiles (Scheme 2).[7–11] Ketenes also engage alkenes in facile, thermally allowed [2 + 2] cycloadditions that share many of the features associated with the imine- and carbonyl-dependent cycloaddition reactions.[12,13] However, alkene cycloadditions wherein ketene ostensibly functions as the electrophilic reaction component, rather than the electron-rich cycloaddition partner for carbonyls and imines, have not, thus far, proven amenable to the development of catalytic asymmetric reaction variants.

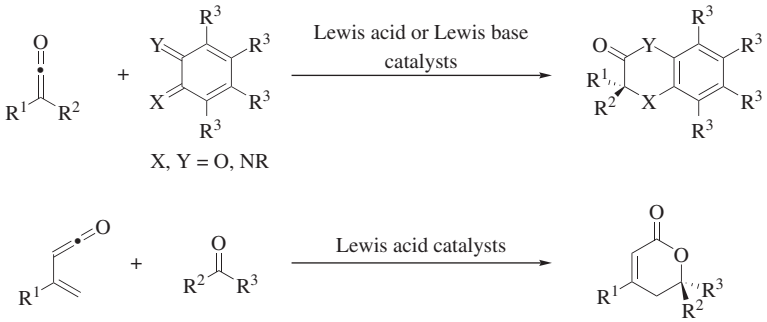


Scheme 1



Scheme 2

The pronounced kinetic preference of ketenes to undergo [2 + 2] cycloadditions, even when competing, higher-order cycloaddition pathways are available, renders [4 + 2] cycloadditions involving ketene reaction partners relatively rare. However, appropriate tuning of the electronic properties of both the ketene and the putative diene or dienophile partner can lead to efficient formal [4 + 2] cycloadditions. In this context, ketene and alkyl-substituted ketenes exhibit reaction profiles characteristic of electron-rich dienophiles and, accordingly, undergo formal [4 + 2] cycloadditions with electrophilic heterodienes in reactions very similar to traditional hetero-Diels–Alder reactions (Scheme 3).[14] Alkenyl-substituted ketenes react similarly to electron-rich dienes in the corresponding [4 + 2] processes and, accordingly, are particularly reactive toward highly electrophilic dienophiles. Moreover, despite the prevalence of [2 + 2] cycloadditions in the chemistry of ketenes, both Lewis acid and Lewis base catalysis can be very effective in diverting ketene reactivity toward higher-order cycloadditions adhering to these reaction design criteria.



Scheme 3

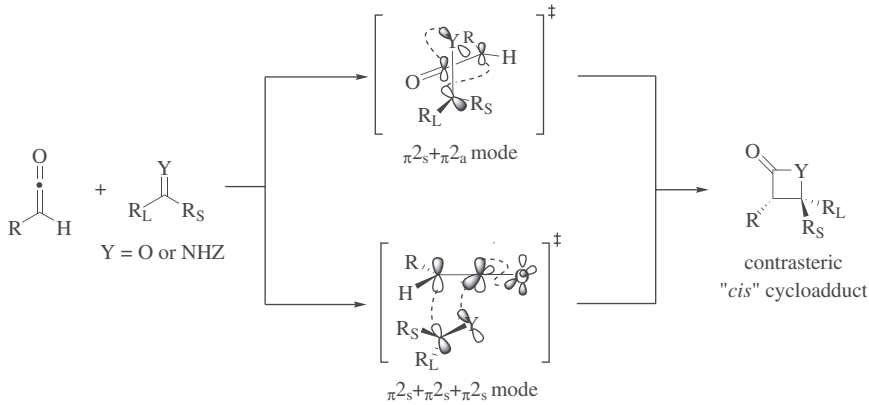
This review presents a comprehensive survey of catalyzed enantioselective ketene [2 + 2] and [4 + 2] cycloadditions in which asymmetric induction is derived solely from the catalyst complex. Diastereoselective cycloadditions are described only when they are relevant to the design, development, or understanding of catalytic asymmetric reaction variants. In this context, the term "cycloaddition" is intended to describe the stoichiometry and structural relationship existing between the reaction starting materials and reaction products

and does not denote the rigorous adherence of these reactions to the pericyclic mechanistic paradigm. Indeed, the majority of catalyzed ketene cycloadditions presented herein proceed through one or more well-defined reaction intermediates and, thus, are not concerted cycloadditions. However, all of these reactions afford products that are, formally, products of [2 + 2] or [4 + 2] cycloadditions and, therefore, are described in this fashion. Many of the studies pertinent to this review appeared nearly concurrently from a number of research groups. Therefore, rather than attempt to present these investigations in rigorous chronological order, the present account organizes these studies according to the type of cycloaddition and the mode of catalysis.

MECHANISM AND STEREOCHEMISTRY

Molecular Orbital Interactions

Orbital-symmetry rules demonstrate ketenes to be ideally suited to function as the antarafacial partners in thermally-allowed $[_{\pi}2_s + {}_{\pi}2_a]$ cycloadditions. The orthogonal approach of ketene and ketenophile required to achieve the correct π-orbital alignment in the four-centered $[_{\pi}2_s + {}_{\pi}2_a]$ transition state is unimpeded by steric interactions due to the sp hybridization at C1 (Scheme 4).[1,2] An alternative Möbius–Hückel analysis of ketene–ketenophile cycloadditions emphasizes the aromatic character achieved in the transition state by involving the ketene carbonyl π-electrons, in addition to the ketene C1–C2 and keteneophile π-bonds.[15] The result is a pericyclic path of six orbitals incorporating six π-electrons with no phase inversions leading to a thermally allowed $[_{\pi}2_s + ({}_{\pi}2_s + {}_{\pi}2_s)]$ process. No definitive experimental distinction exists between these mechanistic alternatives, in part because each model predicts the same diastereoselection with the contrasteric "*cis*" cycloadduct being the predominant product. If the four-centered $[_{\pi}2_s + {}_{\pi}2_a]$ pathway is operative, developing non-bonded interactions in the transition state are minimized when the less sterically demanding substituents



Scheme 4

on both the ketene and ketenophile are oriented toward each other. The offset Möbius–Hückel transition state minimizes incipient steric interactions through a similar juxtaposition of the smaller ketene and ketenophile substituents. Computational modeling of transition states involved in ketene–carbonyl cycloadditions lend support to the $[_{\pi}2_s + (_{\pi}2_s + _{\pi}2_s)]$ model and suggest that it is a combination of steric and stereoelectronic effects that are responsible for the cycloaddition diastereoselection.[16–18] In either case, the emergent heterocycle is predicted to possess a *cis*-relationship of the larger alkyl substituents, in accord with nearly all experimental observations.

Thermal Cycloadditions

The susceptibility of ketenes toward thermal [2 + 2] cycloadditions makes many difficult to insulate from dimerization.[19] Indeed, the exceptionally facile nature of these dimerization processes can render thermal ketene cycloadditions with partners other than itself difficult to achieve in the absence of appropriately chosen reaction conditions or suitable reaction catalysts. Dihaloketenes are especially activated ketenes and possess sufficient reactivity to undergo thermal [2 + 2] reactions with carbonyl and imine partners with limited amounts of competing dimerization. Alternatively, substituted ketenes that are electronically or sterically inhibited toward dimerization can undergo efficient cross-cycloaddition with various carbonyl, imine, or alkene cycloaddition partners (Fig. 1).[20–24]

Figure 1. Representative ketenes deactivated toward dimerization.

Electronic Structure of Ketenes

Although ketenes have available to them a variety of reactivity patterns, they are electronically predisposed toward exhibiting nucleophilic behavior in reactions with electrophilic cycloaddition partners. The ^{13}C NMR spectrum of ketene reveals the C2 resonance at δ 2.5, indicative of significant negative charge localization (Fig. 2).[25] The extraordinary shielding experienced by an sp^2-hybridized carbon suggests that the "enolate-like" resonance form is a significant contributor to the ketene resonance hybrid.[26] In accord with this analysis, ab initio calculations reveal the favorable frontier-molecular-orbital interaction existing between the ketene HOMO and the LUMO of electrophilic cycloaddition partners.[27] Enhancing this HOMO–LUMO interaction, therefore, provides a mechanism for accelerating these reactions in the context of realizing catalytic and, ultimately, asymmetric reaction variants.

Modes of Catalysis

Lewis Acid Catalysis. The mechanisms for catalyzing ketene cycloadditions can be categorized according to the means by which the catalyst enhances the critical HOMO–LUMO interaction. Lewis acid catalysis exploits the intrinsic

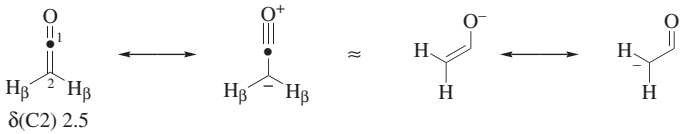


Figure 2. Comparison of ketene and enolate resonance contributors.

nucleophilicity of ketenes by stabilizing the carbonyl π*-orbital through Lewis acid–carbonyl association, thereby enhancing frontier molecular orbital overlap (Fig. 3). Indeed, Lewis acid catalysis is one of the well-established methods for accelerating ketene-carbonyl cycloadditions, leading to highly asynchronous [2 + 2] reactions with substantially advanced C–C relative to C–O bond formation in the transition state (**1**; C–C distance = 2.013 Å, C–O = 2.891 Å).[27–29] The extent to which the zwitterionic aldolate-type structure **2** represents a minimum along this reaction pathway determines the identity of these transformations as true pericyclic [2 + 2] reactions or as stepwise processes leading to formal [2 + 2] adducts.

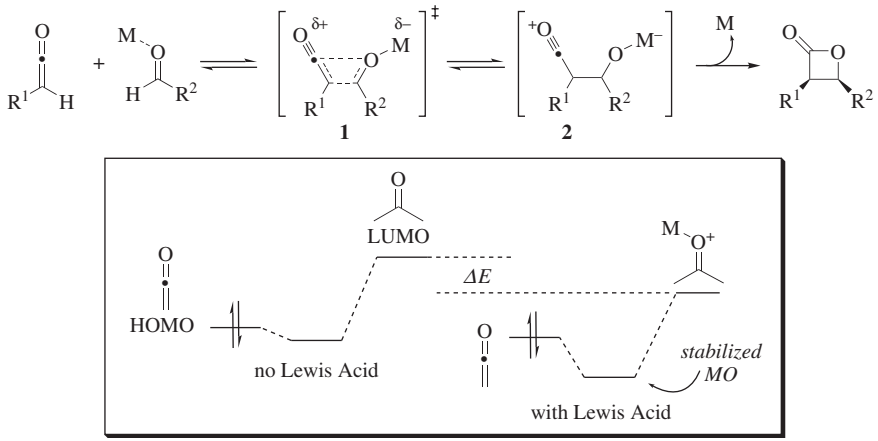


Figure 3. Mechanism for Lewis acid catalyzed ketene–carbonyl [2 + 2] cycloadditions.

Lewis Base Catalysis. Another characteristic ketene reaction manifold originates from pronounced C1 electrophilicity and the accompanying susceptibility toward nucleophilic addition. This reaction mode can be exploited in a "HOMO activation" strategy for catalyzing ketene cycloadditions. Nucleophiles, notably tertiary amines, add to ketenes to generate zwitterionic species **3** resembling enolates; these intermediates further increase C2 electron density and, accordingly, the nucleophilicity expressed by these species toward electrophilic reaction partners (Fig. 4).[30–33] Moreover, a propagating reaction cycle is achieved by ring closure of the aldolate-type intermediate **4** with concomitant liberation of the

Lewis base catalyst in a process that is, definitively, a stepwise, formal [2 + 2] event.[34–36]

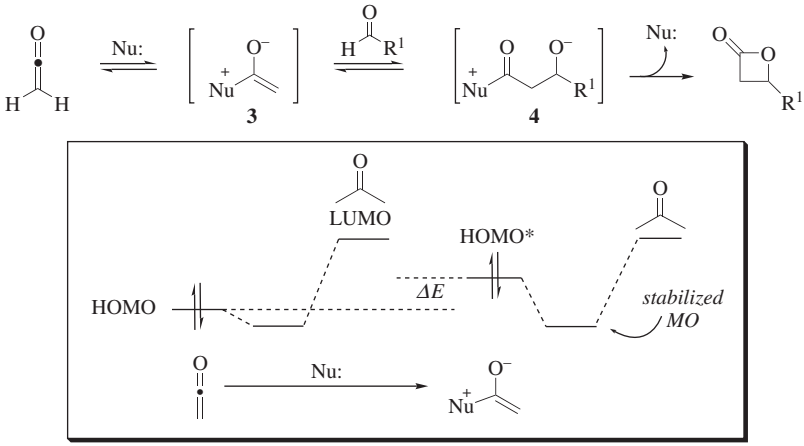
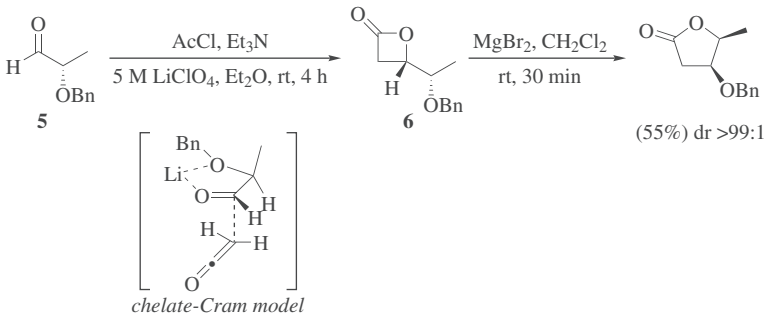


Figure 4. Mechanism for Lewis base catalyzed ketene–carbonyl [2 + 2] cycloadditions.

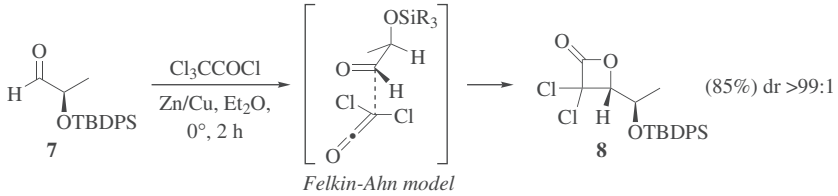
Insights from Diastereoselective Ketene–Carbonyl Cycloadditions

The mechanistic and electronic homology that exists between ketene–carbonyl additions and the related enolate–carbonyl additions suggests that the latter would be susceptible to the well-established stereocontrol elements that exist for aldol and related processes.[37–40] Indeed, diastereoselection in the [2 + 2] cycloaddition of various ketenes with chiral α-substituted aldehydes is consistent with the chelate–Cram and Felkin–Ahn selectivity that dominates nucleophilic additions to chiral, α-substituted aldehydes.[41–43] Thus, [2 + 2] cycloaddition of α-alkoxy aldehyde **5** using $LiClO_4$ as an activator affords the 3,4-*syn*-β-lactone **6** and, ultimately, the *cis*-disubstituted butyrolactone (>99:1 dr) consistent with cycloaddition proceeding via chelate organization (Scheme 5).[18] However, aldehyde **7**, where chelate organization is precluded, affords the 3,4-*anti*-β-lactone **8** (>99:1



Scheme 5

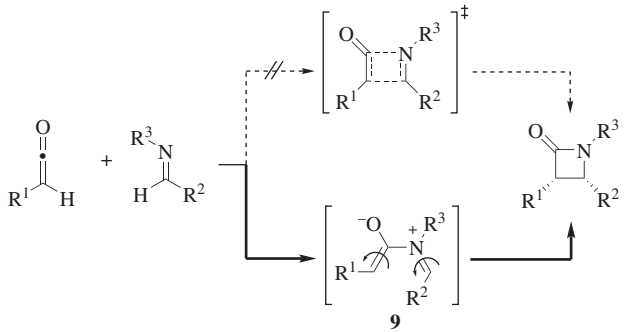
dr) anticipated from Felkin-Ahn selectivity (Scheme 6).[44] These results serve to highlight the veracity of using enolate–electrophile additions as predictive models for analyzing related ketene–carbonyl, or ketene–imine, cycloadditions.



Scheme 6

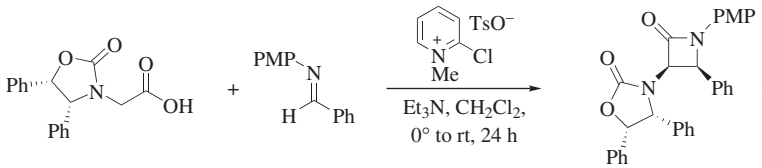
Ketene–Imine Cycloadditions

Staudinger first reported the ketene–imine cycloadditions that would become the most generally useful route to β-lactams.[21] The significance of β-lactams as integral features of frontline antibiotic agents generated considerable interest in refining and broadening Staudinger's original observation as a general route to these heterocycles. The topological homology existing between ketene–carbonyl and ketene–imine [2 + 2] cycloadditions would suggest that the mechanistic details of these transformations are also closely aligned. However, extensive investigations following Staudinger's original reports reveal an alternative mechanistic course, an understanding of which proved critical to Staudinger-type cycloadditions reaching their current level of sophistication (Scheme 7).[30,45,46] Imines possessing Lewis basic nitrogen lone pairs add to ketenes to generate the acyl iminium ion enolate **9**; ensuing electrocyclic ring closure of **9** is then responsible for β-lactam formation. This mechanistic insight proved instrumental in developing effective asymmetric reaction variants as it implicated electrocyclic ring closure as the stereochemically defining event, rather than the putative [2 + 2] cycloaddition process.[47,48]

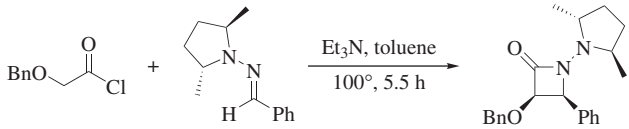


Scheme 7

The influence that these mechanistic insights had on early development of stereoselective Staudinger processes is evident in the early strategies that proved most effective in developing diastereoselective reaction variants. The most successful early examples of asymmetric Staudinger-type reactions utilize chiral auxiliaries or chiral substrates that, following initial imine–ketene addition, influence the stereochemical course of the electrocyclic ring closure event.[46,49] These reaction development strategies, in fact, exploited the electrocyclic ring closure of acyl iminium ion enolate **9** as a facile, thermally-allowed process to achieve efficient diastereoselective cycloaddition. For example, ketenes bearing chiral oxazolidinone auxiliaries (Eq. 1)[50] and enantioenriched hydrazones (Eq. 2)[51,52] are among the most effective ketene and imine reaction components, respectively, for achieving diastereoselective Staudinger reactions via control of the electrocyclic ring closure.



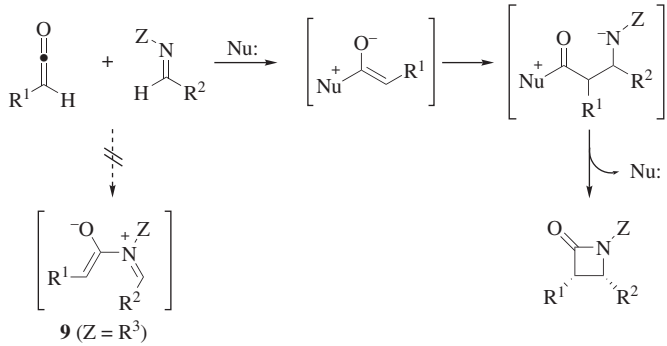
(Eq. 1)



(Eq. 2)

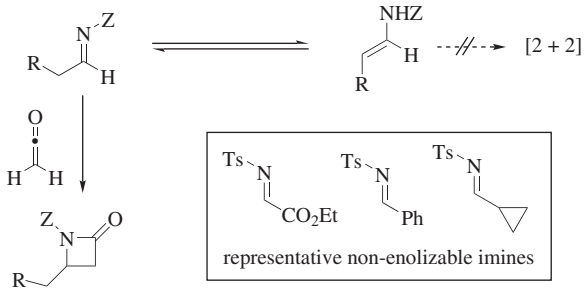
Despite the success realized in developing diastereoselective cycloadditions, electrocyclic ring closure of the acyl iminium ion enolate is not an attractive target for developing the catalyst-dependent reactions required for enantioselective variants due to difficulties inherent in limiting the thermal background reaction rate. However, the mechanisms for catalysis in ketene–carbonyl cycloadditions suggested a strategy for altering the mechanism of these apparent ketene–imine cycloadditions to make them more amenable to catalyst control. Closely related ketene–carbonyl cycloadditions do not involve intermediates related to **9** due to the limited Lewis basicity of the oxygen lone pairs. Thus, derivatizing imine reaction components to attenuate nitrogen lone pair Lewis basicity would, similarly, eliminate the electrocyclic reaction pathway and render ketene–imine cycloadditions mechanistically similar to their ketene–carbonyl counterparts (Scheme 8). Achieving this mechanistic homology would make the ketene–imine cycloadditions subject to Lewis base catalysis and render enolate–imine addition as the stereochemically defining event, rather than electrocyclic ring closure.

Unlike their carbonyl counterparts, aliphatic imines can express a strong tendency toward tautomerization to give the corresponding enamines (Scheme 9).[53] If this tautomerization is fast relative to the enolate addition, the efficiency of the cycloaddition process can be compromised by conversion of the electrophilic imine to the nucleophilic enamine tautomer. As this complication arises only



Scheme 8

for aliphatic imines, much of asymmetric reaction development has focused on non-enolizable imine electrophiles.[49] Indeed, reaction variants implementing these reaction design considerations led to the successful development of Lewis base-catalyzed Staudinger-type reactions providing high levels of catalyst-based stereocontrol.



Scheme 9

[4 + 2] Cycloadditions Involving Ketenes as Dienes or Dienophiles

Evaluating the electronic properties of conjugated ketene systems that constitute diene-like reaction components reveals their marked similarity to the prototypical electron-rich 1,3-dienes used extensively in organic synthesis. The dominant resonance hybrid contributor in conjugated alkenyl ketenes localizes considerable electron density at C4, the same π-system polarization characteristic of traditional electron-rich dienes as observed in Danishefsky's diene **10** (Fig. 5).[54,55] Examples of thermal ketene [4 + 2] cycloadditions are dominated by these alkenyl-substitituted ketenes that function as electron-rich conjugated dienes.[56,57] The reaction mechanisms responsible for the characteristic six-membered [4 + 2] cycloadducts emerging from ketene-derived dienes are strongly dependent on their dienophile partners. Alkyne dienophiles undergo kinetically favored [2 + 2] cycloadditions with an ensuing pericyclic cascade

sequence leading to the formal [4 + 2] cycloadduct in the form of polysubstituted phenols (Scheme 10).[58] Electron-deficient olefins react with alkenyl ketenes to afford cycloadducts exhibiting the *endo* diastereoselection strongly suggestive of a traditional concerted [4 + 2] cycloaddition mechanism (Eq. 3).[59] In accord with their homology with electron-rich dienes, silyl-substituted alkenyl ketenes also engage imines and aldehydes as partners in [4 + 2] cycloadditions affording piperidinone or pyranone cycloadducts, respectively (Eq. 4).[60]

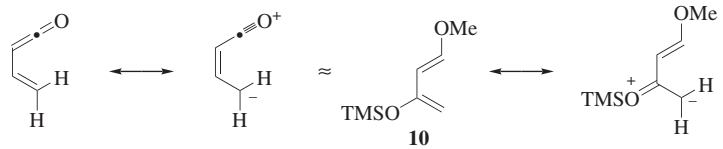
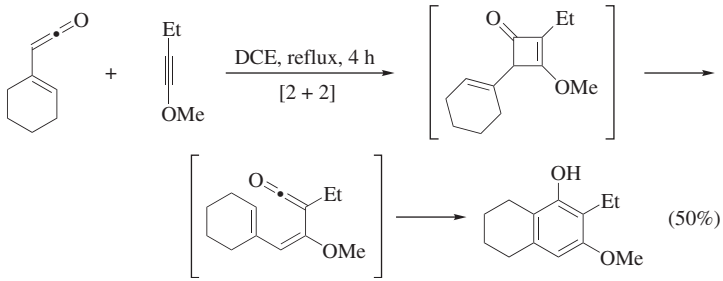
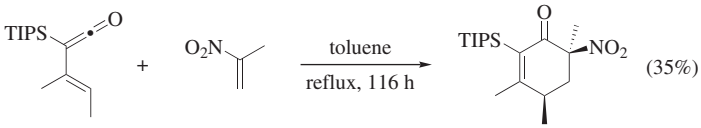


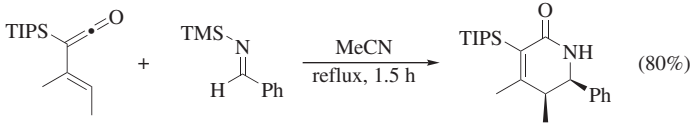
Figure 5. Resonance contributors for alkenyl ketenes and electron-rich 1,3-dienes.



Scheme 10



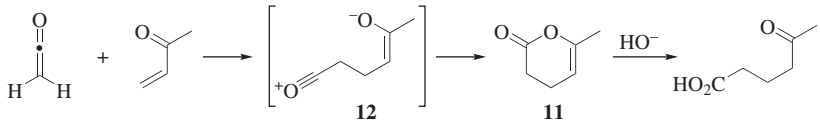
(Eq. 3)



(Eq. 4)

Inverse-electron-demand Diels–Alder cycloadditions again highlight the parallels existing between enolate and ketene reactivity. Ketenes can act as electron-rich dienophiles in formal [4 + 2] cycloadditions with conjugated enone dienes, acting as functional replacements for the electron-rich olefinic dienophiles ordinarily employed in these reactions.[61] Thus, dihydro-2-pyranones (e.g., **11**) emerge from the thermal cycloaddition of ketene and 3-buten-2-one via conjugate addition and ensuing cyclization of the Michael addition adduct **12** (Scheme 11). The

most significant advantage of using ketene in this role derives from the complementary opportunities for the design of catalyzed and, ultimately, asymmetric reaction variants. Developments in catalyzed hetero-Diels–Alder reactions have been dominated by the use of enantioenriched Lewis acids to activate the electrophilic diene. Analogous reactions employing ketenes as dienophiles present both Lewis acid diene activation as well as Lewis base dienophile activation as viable strategies for pursuing catalytic asymmetric reaction variants.

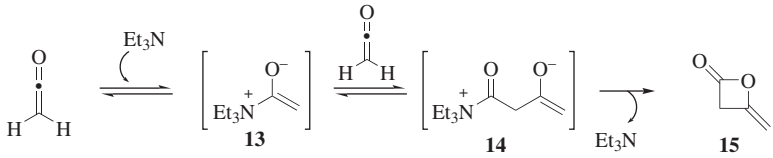


Scheme 11

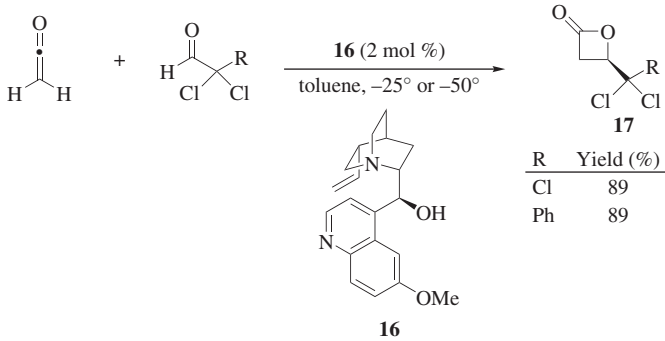
SCOPE AND LIMITATIONS

Lewis Base Catalyzed [2 + 2] Ketene–Carbonyl Cycloadditions

***Cinchona* Alkaloid Catalysis with Activated Aldehydes and Ketones.** Interest in tertiary amines as catalysts for ketene–carbonyl cycloadditions originated with Sauer's observation that ketene dimerization is dramatically accelerated by substoichiometric amounts of triethylamine.[62] Lewis base catalysis originates from amine addition to the ketene to generate a reactive zwitterionic ammonium enolate **13**; enolate–ketene addition affords the aldolate-type intermediate **14** with ensuing lactonization affording the β-lactone ketene dimer **15** with concomitant catalyst regeneration (Scheme 12). In a seminal early example of asymmetric catalysis, Wynberg demonstrated that tertiary amine catalysis is not limited to ketene dimerization and can be applied to ketene–aldehyde cycloadditions.[63–65] *Cinchona* alkaloids are remarkably efficient Lewis basic catalysts for enantioselective cycloadditions of pregenerated ketene with chloral and other α,α-dichloroaldehydes (Scheme 13).[64] Bubbling ketene gas into toluene solutions of these highly electrophilic aldehydes and quinidine (**16**) (2 mol %) delivers the corresponding β-lactones **17** with high enantioselectivity (>90% ee). Methyl trichloromethyl ketone and various aryl trichloromethyl ketones participate in similarly efficient and equally enantioselective cycloadditions with ketene using quinidine as catalyst to afford the 4,4-disubstituted 2-oxetanones such as **18** (89–94% ee) (Eq. 5).[64] Alkyl trichloromethyl ketones possessing alkyl substituents other than methyl are not effective substrates for these cycloadditions, suggestive of the severe steric constraints present in ketene–ketone cycloadditions. The fact that quinidine (**16**) and quinine (**19**) are diastereomeric and, therefore, need not perform identically as reaction catalysts is evidenced by the considerable erosion in cycloaddition enantioselection observed for reactions employing quinine as catalyst (Scheme 14).[64]

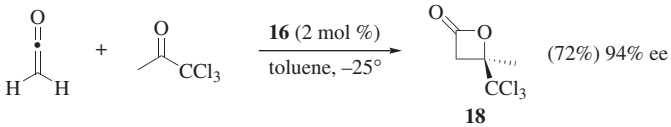


Scheme 12

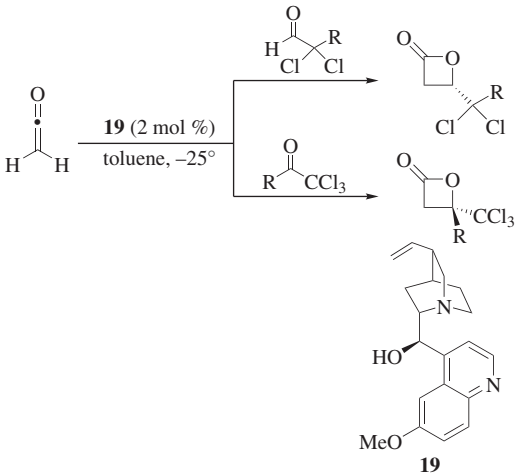


R	Yield (%)	ee (%)
Cl	89	98
Ph	89	90

Scheme 13



(Eq. 5)

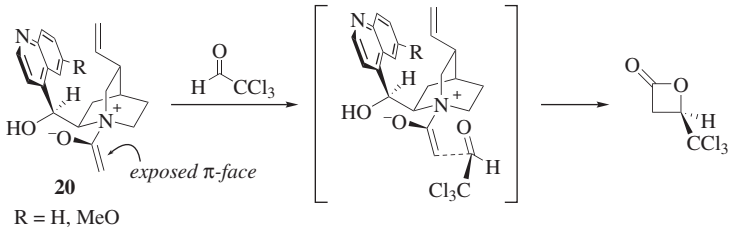


R	Yield (%)	ee (%)
Cl	89	76
Me	95	76

R	Yield (%)	ee (%)
Me	72	85
4-ClC_6H_4	68	65

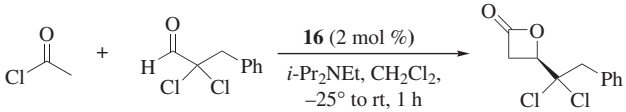
Scheme 14

In accord with Sauer's mechanistic hypothesis regarding ketene dimerization, tertiary amine-mediated catalysis of the ketene–chloral cycloadditions is attributed to formation of the enantioenriched zwitterionic enolate **20** wherein the alkaloid residue confers sufficient transition state organization to realize near perfect enantioselection (Scheme 15).[8] A model rationalizing enantioselectivity indicates that the enantioenriched ammonium enolate adopts a conformation maximizing π-stacking between the enolate and quinoline π-systems. Approach of the aldehyde *re* face to the exposed face of the enolate provides the observed β-lactone enantiomer. Subsequent computational studies on zwitterionic enolate structures in related *cinchona* alkaloid-catalyzed ketene–imine additions affords confirmatory evidence for this analysis.[8,66]



Scheme 15

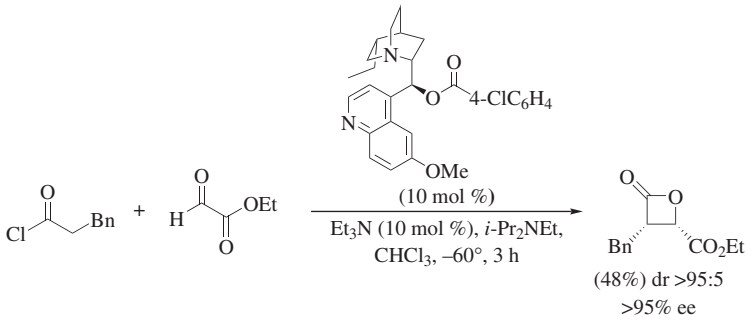
Subsequent to Wynberg's pioneering work, reaction conditions were developed allowing these same alkaloid-catalyzed cycloadditions to be achieved using ketene that is generated in situ, thereby relieving the requirement for pregenerating gaseous ketene (Eq. 6).[67] Thus, adding acetyl chloride to a dichloromethane solution of 2,2-dichloro-3-phenylpropanal, *N*,*N*-diisopropylethylamine, and alkaloid catalyst **16** (10 mol %) provides the cycloadduct β-lactone that parallels those obtained from the original Wynberg reactions in both structure and enantioselectivity. Ethyl glyoxylate functions similarly as a highly electrophilic ketenophile, reacting with in situ generated ketenes under alkaloid catalysis to afford the *cis*-disubstituted β-lactone with very high enantio- and diastereoselectivity, albeit in moderate yield (Eq. 7).[68]



(85%) 94% ee (Eq. 6)

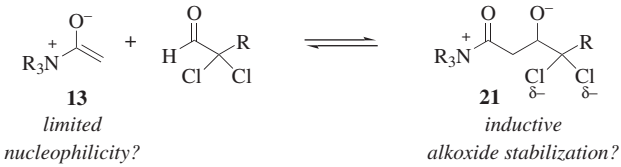
Amine-mediated dehydrohalogenation of acyl halides constitutes the most convenient and cost-effective method for ketene generation. While a variety of Brønsted bases are suitable for this purpose, integrating this method for ketene generation with Lewis base catalysis requires that the auxiliary base does not effectively compete with the enantioenriched catalyst for ketene activation.[3,69] Accordingly, the limited nucleophilicity expressed by *N*,*N*-diisopropylethylamine, combined with its ready availability, has made it the most popular

choice for catalytic asymmetric ketene cycloadditions integrating in situ ketene generation.



(Eq. 7)

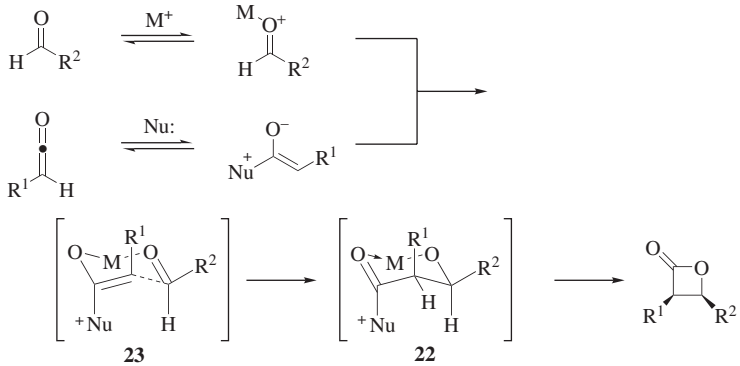
Alkaloid-Catalyzed [2 + 2] Cycloadditions of Unactivated Aldehydes. Wynberg's alkaloid-catalyzed ketene–aldehyde cycloadditions are among the earliest and most successful, and often underappreciated, examples of the increasingly important field of organocatalysis.[70] Despite the landmark stature of the Wynberg cycloadditions, their utility in organic syntheses is limited by the requirement for non-enolizable, highly activated α,α-dichloro carbonyl substrates and the need to pregenerate gaseous ketene. The development of *cinchona* alkaloid–Lewis acid co-catalyst systems to address these limitations ultimately yielded an attractive source of structurally diverse enantioenriched β-lactone building blocks. An analysis of the Wynberg cycloaddition reaction mechanism suggested an explanation for the requirement for highly electrophilic aldehydes and provided inspiration for examining alkaloid catalysts augmented by Lewis acid addends. First, the putative zwitterionic enolate intermediates are expected to possess attenuated nucleophilicity relative to prototypical enolate nucleophiles due to the inductive stabilization afforded the enolate anion by the pendant ammonium ion (Scheme 16). Also, addition of enolate **13** to the aldehyde electrophile proceeds with increased charge separation that contributes to destabilization of the putative aldolate intermediate **21**, rendering inductive stabilization of the developing alkoxide provided by strongly electron-withdrawing aldehyde electrophiles essential for an efficient reaction.



Scheme 16

Lewis acid addends to the alkaloid-catalyzed ketene–aldehyde cycloadditions offer a solution to both limited enolate nucleophilicity and aldolate stability.

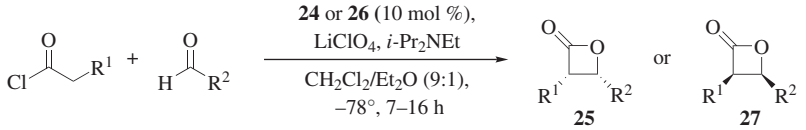
Lewis acid co-catalysts are expected to enhance aldehyde electrophilicity derived from Lewis acid–base association, provided alkaloid–Lewis acid association does not provide a mechanism for catalyst poisoning. Moreover, enolate addition to the Lewis acid coordinated aldehyde would deliver aldolate **22**, benefiting from enhanced stability afforded by bidentate metal coordination (Scheme 17). Furthermore, the reaction of the zwitterionic enolate with a Lewis acid activated aldehyde offers the possibility of C–C bond construction proceeding through a closed, metal-templated transition state, wherein the Lewis acid is responsible for both aldehyde activation and enolate stabilization, leading to a Zimmerman–Traxler type transition state **23**.[71]

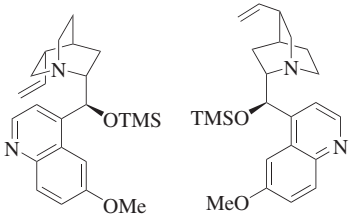


Scheme 17

This reaction design is successfully implemented in developing alkaloid-catalyzed cycloadditions of in situ generated ketenes with structurally diverse and unactivated aldehyde partners.[72] Catalyst optimization studies reveal that *O*-trimethylsilylquinidine (**24**) in conjunction with $LiClO_4$ (or LiI) provides the optimized catalyst system for highly enantioselective cycloadditions of ketene or alkyl-substituted ketenes to a variety of aldehydes (Scheme 18).[72] Under these conditions, easily enolizable, sterically hindered, and functionalized aldehydes afford the β-lactones **25** from highly enantioselective (92–99% ee) and, in the case of substituted ketenes, diastereoselective [2 + 2] cycloadditions. The catalytic competency of the pseudoenantiomeric Lewis base catalyst *O*-trimethylsilylquinine (**26**) parallels closely that of **24**, thereby providing convenient access to the enantiomeric β-lactones **27** (96–99% ee). The potential for competing ketene dimerization, another process catalyzed by alkaloid Lewis bases, is minimized in these reactions by syringe pump addition of the acyl chloride to a solution containing the catalyst, tertiary amine, lithium salt, and aldehyde.

The sense of enantioselection observed in these cycloadditions is interpreted in the context of the proposed mechanism involving a lithium-centered closed transition state (Scheme 19).[72] The reactive conformation of the alkaloid-derived zwitterionic enolate is that originally proposed for the related Wynberg

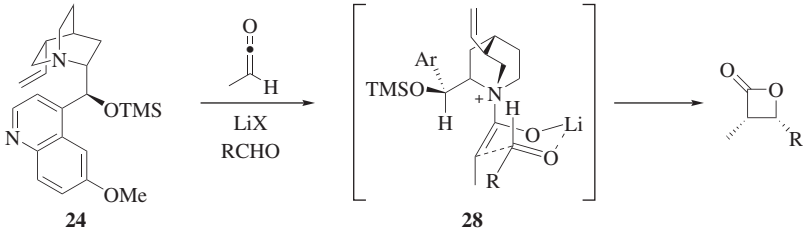




Catalyst	R^1	R^2	Yield (%) **25**	Yield (%) **27**	ee (%)
24	H	*t*-Bu	71	—	96
24	Me	*c*-C_6H_{11}	74	—	97
26	Me	$PhCH_2CH_2$	—	84	>99
26	Me	Ph	—	78	>99

Scheme 18

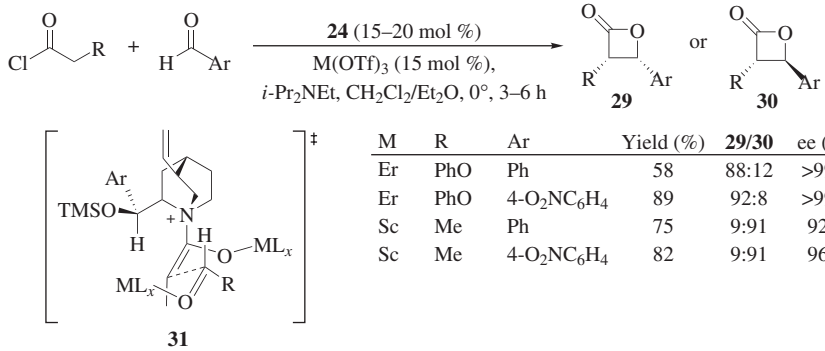
ketene–chloral cycloadditions. The close homology that exists between the putative lithium-centered transition state **28** and aldol additions proceeding via Zimmerman–Traxler-type transition states dictates that the aldehyde is delivered from the exposed enolate π-bond face with the alkyl substituent occupying a pseudo equatorial position.[71] Circumstantial support for this mechanistic hypothesis is derived from subsequent studies that reveal that double diastereoselection is operative in ketene cycloadditions involving enantioenriched aldehyde substrates.



Scheme 19

The rigorous *cis*-diastereoselection obtained from the alkaloid-catalyzed ketene–aldehyde cycloadditions can be reversed for aryl aldehyde electrophiles by proper selection of Lewis acid addend. Using erbium triflate as the Lewis acid co-catalyst (15 mol %), the cycloaddition of phenoxyketene and aryl aldehydes exhibits the typical *cis*-diastereoselection using *O*-trimethylsilylquinidine (**24**, 20 mol %) as catalyst in yielding β-lactones **29** (Scheme 20).[73] However, methyl- and ethylketene in conjunction with scandium triflate afford predominately the *trans*-4-aryl-2-oxetanones **30**. This reversal in diastereoselection is interpreted as originating from C–C bond construction occurring via open transition state

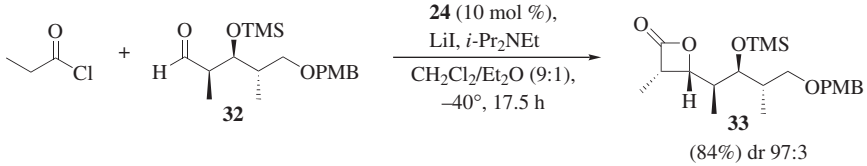
31, wherein separate Lewis acid moieties coordinate both the aldehyde and the ketene-derived enolate.[74]



M	R	Ar	Yield (%)	**29/30**	ee (%)
Er	PhO	Ph	58	88:12	>99
Er	PhO	4-$O_2NC_6H_4$	89	92:8	>99
Sc	Me	Ph	75	9:91	92
Sc	Me	4-$O_2NC_6H_4$	82	9:91	96

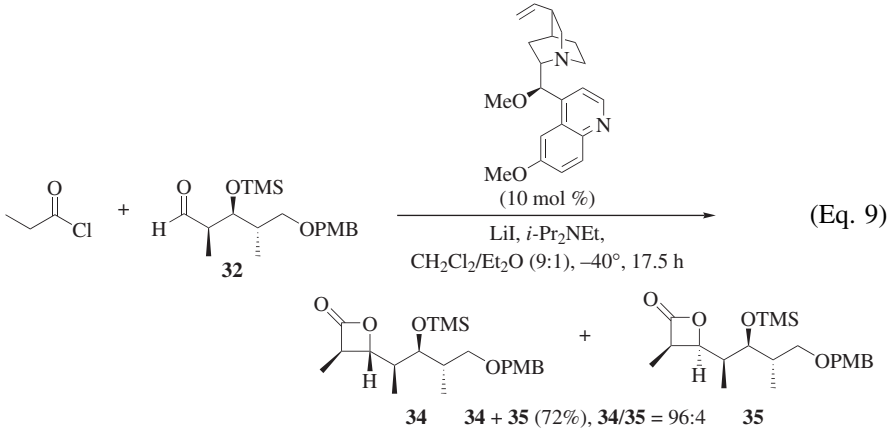
Scheme 20

The *cinchona* alkaloid–Li(I) co-catalyst systems also allow structurally and stereochemically complex aldehydes to be employed as substrates in the asymmetric ketene cycloadditions.[75] For example, the enantioenriched aldehyde **32** participates in the highly diastereoselective cycloaddition with methyl ketene under the quinidine-LiI conditions to afford the β-lactone **33** with very high diastereoselectivity (Eq. 8).[75] The combined effect of catalyst and substrate chirality is at issue in these double diastereoselective cycloadditions and it is presumed that the quinidine-catalyzed reaction of **32** with methyl ketene constitutes a matched pairing of catalyst and aldehyde chirality.[76] Evidence that both catalyst and substrate chirality are important to the stereoselectivity observed in these double diastereoselective cycloadditions is provided by the reaction of aldehyde **32** with the pseudoenantiomeric *O*-methylquinine catalyst, an ostensibly mismatched catalyst–substrate pairing (Eq. 9).[75] Thus, the reaction of **32** with methyl ketene using *O*-methylquinine as catalyst affords the β-lactone **34**, the first example of an alkaloid-catalyzed cycloaddition affording a *trans*-disubstituted β-lactone with high diastereoselectivity. The fact that neither *syn*-β-lactone **35** expected for a catalyst-controlled reaction nor lactone **33**, presumed favored by substrate-based stereocontrol, predominate in these reactions is clearly indicative of the interplay existing between substrate and catalyst chirality.



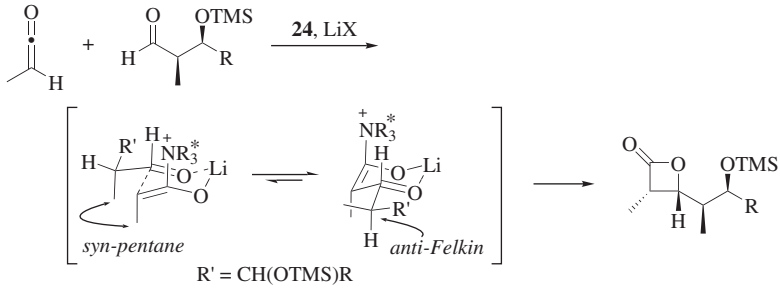
(84%) dr 97:3

(Eq. 8)

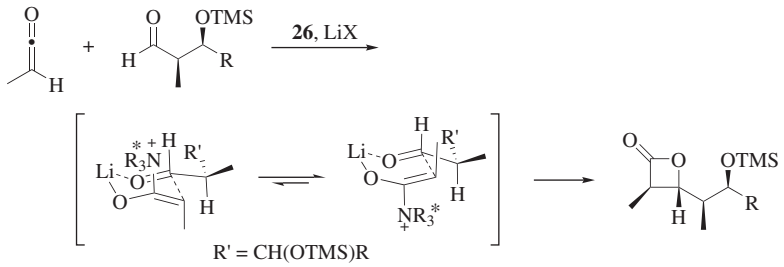


(Eq. 9)

This pattern of double diastereoselection is interpreted as arising from C–C bond construction proceeding through a closed transition state that shares considerable homology with aldol additions adhering to Zimmerman–Traxler transition state organization.[71] Accordingly, the (*Z*)-acylammonium ion enolate expresses a preference for anti-Felkin addition to the α-substituted aldehyde, thereby avoiding the developing *syn*-pentane interaction incurred in Felkin addition to the α-substituted aldehyde (Scheme 21).[37] Within this ensemble, the quinidine-derived enolate can present the exposed enolate diastereoface to the aldehyde leading to matched catalyst- and substrate-based stereocontrol. The privileged nature of *cinchona* alkaloids as Lewis basic catalysts for ketene cycloadditions is reaffirmed in these reactions as a variety of achiral amine additives are dramatically inferior catalysts with regard to reaction efficiency and chemical yield. Cycloaddition diastereoselection achieved using quinine-derived catalysts is consistent with the aldehyde continuing to express anti-Felkin facial bias during carbonyl addition; however, in order for the alkaloid-derived enolate to avoid exposing the disfavored enolate diastereoface to the aldehyde, the enolate adds via a closed, boat-like transition structure delivering the observed diastereoselection (Scheme 22).

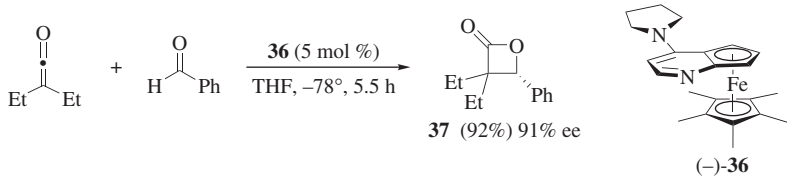


Scheme 21

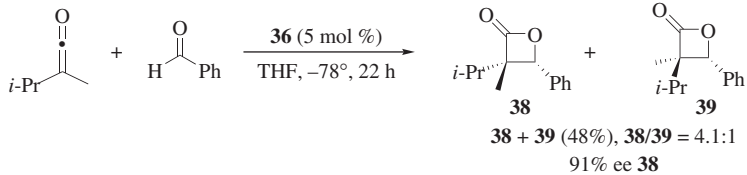


Scheme 22

Fe(II)–Azaindene Catalysts for Ketene–Aldehyde Cycloadditions. Although *cinchona* alkaloids represent the most widely investigated catalysts for ketene-based cycloaddition reactions, enantioselective Lewis base catalysis of ketene–aldehyde cycloadditions is not exclusive to these naturally occurring alkaloids. Iron(II)-4-azaindene complexes have been developed as enantioenriched equivalents of 4-dimethylaminopyridine, a ubiquitous Lewis basic amine catalyst.[77,78] The Lewis basicity expressed by 4-(pyrrolidino)pyridine complex **36** renders it an excellent catalyst for the enantioselective cycloaddition of dialkyl ketenes with aryl aldehydes.[79] Thus, symmetrically disubstituted ketenes react with aryl aldehydes using complex **36** (5 mol %) as catalyst to afford β-lactone **37** with relatively high enantiomeric excess (Eq. 10).[79] Unsymmetrically disubstituted ketenes react similarly with aryl aldehydes producing β-lactones with high absolute stereocontrol and moderate diastereoselectivity as illustrated by the distribution of β-lactone products **38** and **39** in Eq. 11.[79] Low reaction temperatures (−78°) are essential for successful reactions; under otherwise identical conditions, β-lactones are not obtained from reactions conducted at ambient temperature. Moreover, the Fe(II)-azaindene catalysts offer reactivity that is unavailable from the commonly utilized alkaloid derivatives as the latter are completely ineffective at engaging disubstituted ketenes in analogous cycloadditions.

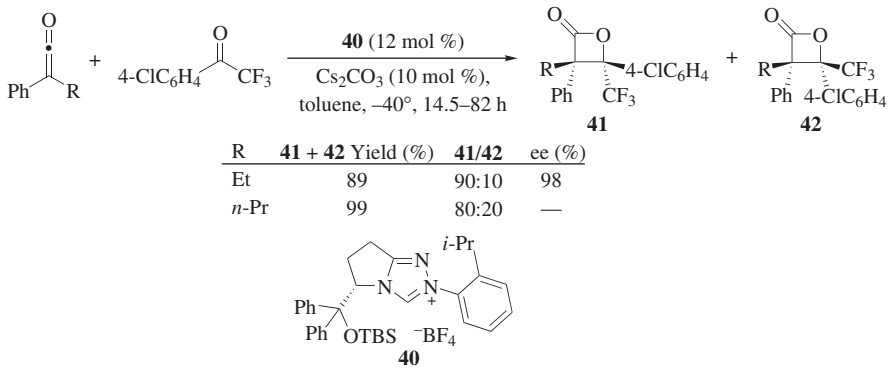


(Eq. 10)



(Eq. 11)

Heterocyclic Carbene Catalysis with Trifluoromethyl Ketones. Although *cinchona* alkaloids and the Fe(II)-azaindenes are uniquely effective catalysts for ketene–carbonyl cycloaddition reactions, ketene cycloaddition catalysis by the HOMO-activation mechanism is not limited to amine Lewis bases. Indeed, any Lewis basic entity capable of producing the requisite zwitterionic enolate intermediate operative in the Lewis base catalyzed reactions represents a viable catalyst candidate. Accordingly, triazolium-type carbenes, species whose reactivity is primarily defined by their Lewis basic non-bonding electron pair, have demonstrated activity as catalysts for ketene–carbonyl [2 + 2] cycloadditions. In fact, enantioenriched triazolium-derived carbenes (e.g., the carbene generated from **40**) are unique among Lewis basic catalysts for ketene cycloadditions in their ability to mediate the stereoselective construction of vicinal quaternary carbon stereocenters via the reaction of alkyl aryl ketenes with aryl trifluoromethyl ketones (Scheme 23).[80] Aryl trifluoromethyl ketones exhibit sufficient electrophilicity to undergo addition by carbene-activated ketene enolates to afford tetrasubstituted β-lactones **41** and **42** with generally good diastereoselectivity (80:20 to >95:5) and uniformly high enantioselectivity (91–99% ee). Reaction enantioselection is modestly responsive to the structure of the *N*-aryl substituent on the carbene with optimal enantioselectivity being attained with *ortho*-substituted aryl groups. Using the optimized carbene catalyst derived from **40** (12 mol %), cycloadditions perform well for aryl methyl and aryl ethyl ketenes, whereas diasteroselectivity is eroded for larger alkyl substituents. Ketenes possessing branched alkyl substituents or sterically demanding aryl substituents, such as *ortho*-substituted aromatic groups, do not participate in these reactions.

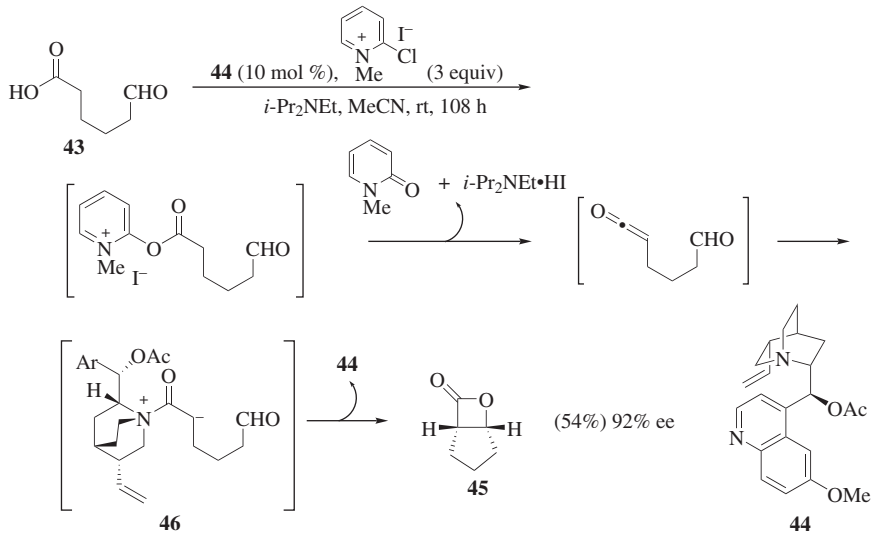


R	**41** + **42** Yield (%)	**41**/**42**	ee (%)
Et	89	90:10	98
n-Pr	99	80:20	—

Scheme 23

Intramolecular Ketene–Aldehyde [2 + 2] Cycloadditions. Intramolecular Wynberg-type cycloadditions have also been examined as a means of overcoming the original requirement of this reaction for highly activated aldehydes.[81–83] Indeed, the reduced entropic penalty associated with intramolecular reactions often provides a mechanism for overriding unfavorable reaction enthalpy.

Thus, syringe pump addition of carboxylic acid aldehyde **43** to a mixture of di(isopropyl)ethylamine, *N*-methyl-2-chloropyridinium iodide (3 equiv) and *O*-acetylquinidine (**44**) (10 mol %) delivers the bicyclic β-lactone **45** with high enantioselectivity and in moderate yield (Scheme 24).[81] The reaction proceeds by initial activation of the carboxylic acid as the corresponding acyloxypyridinium ion; amine-mediated pyridone elimination affords the ketene intermediate required for the alkaloid-catalyzed cycloaddition via enolate **46**. Enantioselectivity in these annulations directly parallels that obtained from analogous intermolecular reactions that employ quinidine as the catalyst.

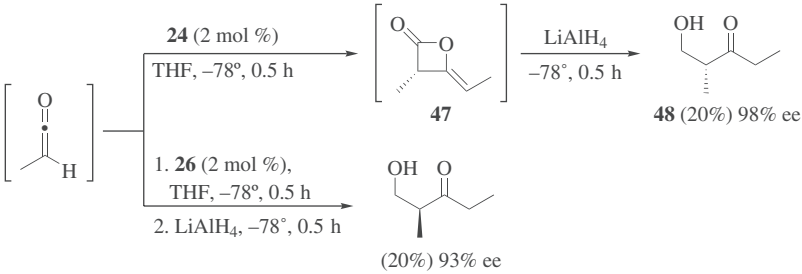


Scheme 24

Catalytic Asymmetric Ketene Dimerization

***Cinchona* Alkaloid Catalysts.** The synergy between Sauer's original observations and Wynberg's development of Lewis basic catalysts in ketene-based cycloadditions undoubtedly provided inspiration for the development of *cinchona* alkaloid-catalyzed, asymmetric ketene dimerization reactions (Scheme 25).[84] Adding solutions of methylketene, pregenerated by pyrolysis of propionic anhydride[85] or zinc-mediated dehalogenation of 2-bromopropionyl bromide,[22,86] to *O*-trimethylsilylquinidine (**24**) provides the enantioenriched ketene dimer **47**. The reactivity and volatility of **47** dictates that the cycloadduct is isolated as the corresponding β-keto alcohol **48** obtained by hydride-mediated reduction of the enantioenriched ketene dimer (98% ee). Dimerization enantioselection is optimal using quinidine derivative **24** as the catalyst; reactions catalyzed by *O*-trimethylsilylquinine (**26**) afford nearly equal, but opposite, enantioselection. The performance of the diastereomeric *O*-silylated catalysts **24** and **26** as pseudoenantiomers in these dimerizations represents a significant

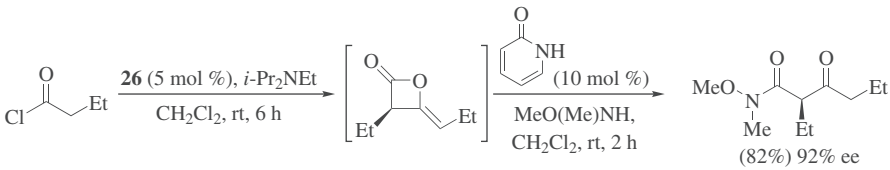
observation considering pronounced differences in enantioselectivity obtained in the quinidine- and quinine-catalyzed Wynberg-type cycloadditions.



Scheme 25

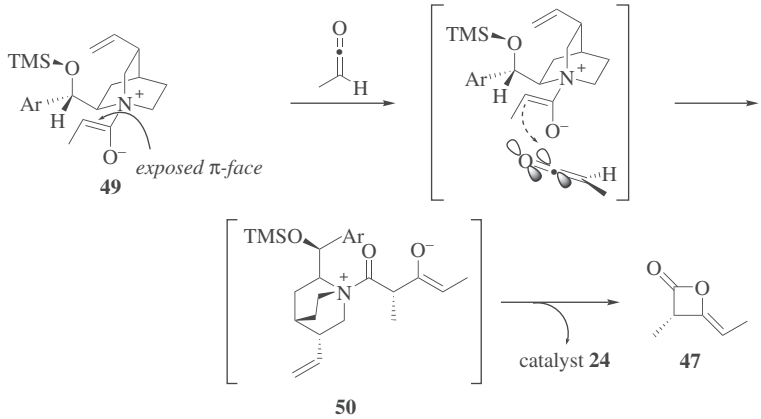
To achive high enantioselectivity in the alkaloid-catalyzed ketene dimerizations requires the generation of ketene under conditions that limit competing thermal dimerization. Propionic anhydride thermolysis generates methylketene gas that can be bubbled into precooled organic solvents to afford solutions free of contaminants that might promote dimerization.[85] However, the Zn(II) bromide byproduct of zinc-mediated debromination of 2-bromopropionyl bromide can assist in accelerating ketene dimerization if it is not effectively removed from the resulting ketene solutions.[86] Thus, methylketene is obtained from the reductive debromination reactions by distilling the ketene–THF azeotrope prior to introduction into the cycloaddition reaction.[86]

Catalytic asymmetric ketene dimerizations can be extended to other alkyl-substituted ketenes using in situ ketene generation.[87,88] Amine-mediated dehydrohalogenation of acyl chlorides is merged with alkaloid-catalyzed ketene dimerization to afford dimers with enantioselectivities only modestly attenuated relative to the methylketene dimerizations (Scheme 26).[87] Under these conditions, a variety of functionalized acyl halides participate in the ketene dimerization reaction to afford enantioenriched β-lactone dimers. These dimers can be isolated or converted in situ into the enantioenriched β-keto amides by reaction with *N*,*O*-dimethylhydroxylamine using 2-pyridone as the catalyst.



Scheme 26

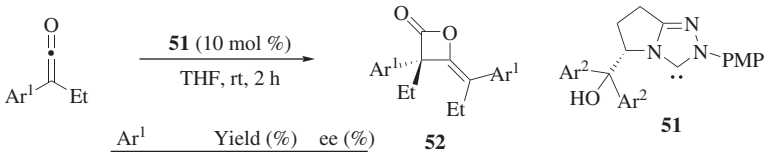
A model slightly modified from that proposed by Wynberg is suggested as a rationale for asymmetric induction in the *O*-trimethylsilyquinidine-catalyzed ketene dimerizations (Scheme 27).[84] The reactive zwitterionic enolate **49** adopts a conformation that minimizes C–O dipole–dipole interactions, or alkoxide–silyloxy steric interactions, dictating an *anti*-orientation of the C9 alkoxy group and enolate oxygen wherein the quinoline ring adopts the sterically least-congested orientation. Approach of the ketene to the exposed enolate *Re* diastereoface is in accord with the stereochemical outcome of the dimerizations. The observed olefin geometry in the β-lactone cycloadduct is consistent with addition of the (*Z*)-zwitterionic enolate **49** to the ketene carbonyl π-face *syn* to the smaller C2 substituent (hydrogen) to afford the (*Z*)-configured aldolate intermediate **50** as a direct precursor to ketene dimer **47**.



Scheme 27

1,2,4-Triazolium Carbene Catalysts. The ability of heterocyclic carbene Lewis bases to access the corresponding ketene-derived enolates renders these species as effective catalysts for the asymmetric dimerization of disubstituted ketenes. The 1,2,4-triazole-derived carbene **51** catalyzes the enantioselective dimerization of alkyl aryl ketenes to afford the β-lactone dimers **52** as single geometric isomers with generally high enantioselectivity; the β-lactone product of ethylphenylketene dimerization is formed in 96% ee (Scheme 28).[89] Methylphenylketene incorporating a methyl substituent rather than longer chain alkyl groups (i.e., Et or *n*-Bu) affords modestly reduced enantioselectivity (~84% ee) whereas *ortho*-substituted aryl ketenes are not useful substrates (0–46%, ~28% ee). Despite these limitations, carbene catalysts enable enantioselective dimerizations of disubstituted ketenes, reactions that fail using the *cinchona* alkaloid catalysts used to prepare monosubstituted ketene dimers.

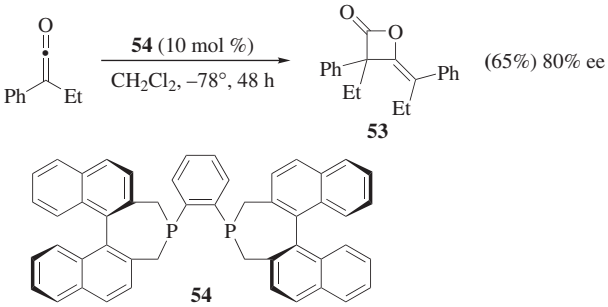
Phosphine Catalysts. Parallels between the reactivity of trialkylamines and trialkylphosphines as Lewis bases suggest phosphines should provide alternatives



Ar^1	Yield (%)	ee (%)
Ph	83	96
2-ClC_6H_4	trace	—

Scheme 28

to tertiary amines as catalysts for ketene-based cycloadditions. Indeed, trialkyl phosphites and trialkyl or triaryl phosphines are used as catalysts for the dimerization of dialkyl ketenes.[90,91] These investigations have led to a single example of an asymmetric ketene dimerization catalyzed by enantioenriched phosphine catalyst **54**, although the configuration of β-lactone **53** is not reported (Eq. 12).[90]



(Eq. 12)

Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloadditions

A strategy for catalyzed ketene cycloadditions complementary to Lewis base catalyzed variants emerges from reaction designs targeting Lewis acid activation of the electrophilic reaction component rather than ketene activation.[92,93] Despite the success of Lewis base catalyzed ketene cycloadditions, catalyst-dependent ketene dimerization or oligomerization can present a complicating factor in the targeted ketene–aldehyde, or ketene–imine, cycloadditions. Ketenes are relatively weak oxygen Lewis bases due to the significant contribution of the "enolate-like" resonance form, rendering them ineffective ligands for typical Lewis acid addends (Fig. 6).[94,95] As a result, this LUMO activation mechanism for catalysis does not dramatically accelerate competing thermal ketene dimerization. Moreover, the comparable Lewis basicity of the β-lactone cycloadduct and the monodentate aldehyde substrate functions to render catalyst turnover unencumbered by extensive product inhibition.

Al(III)-Catalyzed Reactions Involving Pregenerated Ketenes. The first efforts toward realizing catalytic asymmetric Lewis acid catalyzed ketene–aldehyde cycloadditions employed the Al(III)–BINOL complex **55** as a

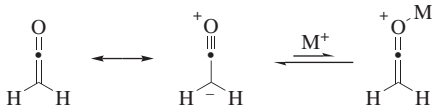
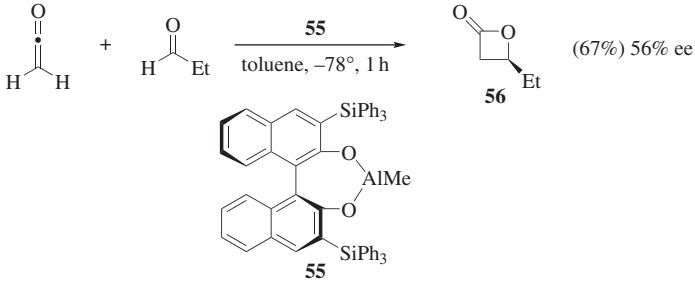


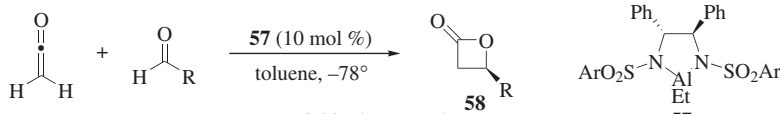
Figure 6. Ketene resonance contributors: implications for oxygen Lewis basicity.

stoichiometric promoter for cycloadditions using pregenerated ketene (Eq. 13).[96] Adding a toluene solution of ketene, generated by bubbling freshly generated gaseous ketene into toluene, to a solution containing the Al(III) complex **55** (1 equiv) and the aldehyde delivers the corresponding β-lactone **56** in moderate yield and modest enantioselectivity (56% ee).[96] Typically, enantioselectivities range from 17–56%. An attempt to use **55** in substoichiometric amounts (10 mol %) fails to afford any ketene–aldehyde cycloaddition.



(Eq. 13)

Greater substrate generality in Al(III)-catalyzed ketene–carbonyl cycloaddition is realized using the Al(III)–bis(sulfonamide) complex **57** (Scheme 29).[97] In contrast to the BINOL-derived Al(III) complex **55**, the bis(sulfonamide) **57** delivered the desired 2-oxetanones **58** in generally good yields for a range of aldehydes (11–94%) with enantioselectivity remaining modest (0–74% ee). Despite these limitations, these investigations established, for the first time, the potential for Lewis acid catalysis to deliver significant levels of enantioselection in ketene–aldehyde [2 + 2] cycloadditions.



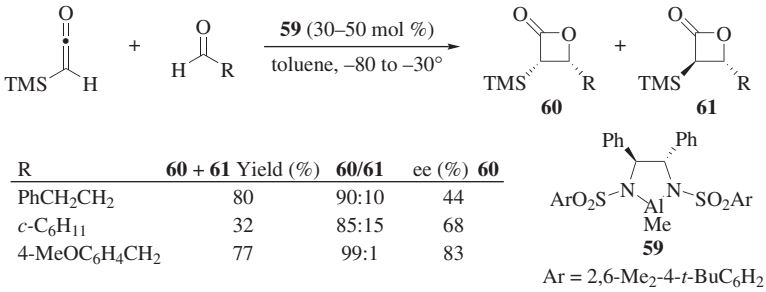
R	Yield (%)	ee (%)
Et	77	33
c-C_6H_{11}	75	74

Scheme 29

Al(III)-Catalyzed Reactions Involving Trimethylsilylketene. Reaction designs involving ketene substrates must incorporate mechanisms for mitigating

the marked propensity of most ketenes to undergo thermal dimerization. Trimethylsilylketene is shelf-stable and commercially available and, therefore, is an especially convenient reagent for developing ketene-based reactions.[98] Trimethylsilylketene is the prototype of the family of ketenes that are electronically or sterically shielded from undergoing thermal dimerization. As a result, tedious procedures or special equipment required for ketene generation are not required for trimethylsilylketene-based cycloadditions. Cycloadducts derived from trimethylsilylketene offer the additional advantage of possessing a stereodefined α-trimethylsilyl carbonyl functionality, although this functionality is rarely exploited in ensuing synthesis activities.[99]

These attributes of trimethylsilylketene certainly contributed to the significant efforts devoted to developing asymmetric Lewis acid catalyzed cycloadditions of aldehydes using this ketene as the nucleophilic reaction partner. Following the success of the Al(III)–bis(sulfonamide) **57** as a catalyst for ketene–aldehyde cycloadditions, closely related catalyst complexes find utility in ketene–aldehyde cycloadditions employing trimethylsilylketene (Scheme 30).[100] Thus, the reactions of trimethylsilylketene with various aliphatic aldehydes using relatively high loadings of Al(III)–bis(sulfonamide) **59** (30–50 mol %) deliver the diastereomeric 3-trimethylsilyl-4-alkyl-2-oxetanones **60** and **61** with the *cis* diastereomer predominating (30–83% ee). In these reactions, relative and absolute stereocontrol proved to be quite sensitive to aldehyde structure with the best results being obtained for 4-methoxyphenylacetaldehyde (83% ee, 98% de). Absolute and relative stereocontrol are considerably lower for other aliphatic aldehydes. Aryl aldehydes are not useful cycloaddition partners, presumably due to the sensitivity of the derived 4-aryl-2-oxetanones toward C4-O bond heterolysis, especially under the Lewis acidic reaction conditions.

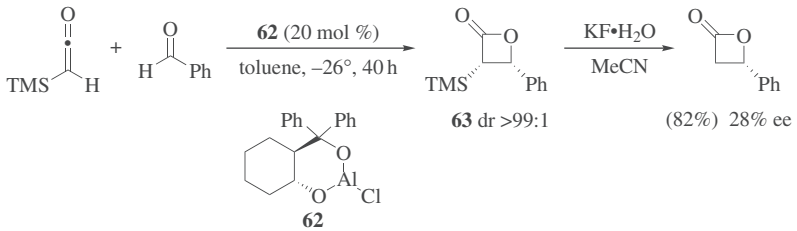


R	**60** + **61** Yield (%)	**60/61**	ee (%) **60**
$PhCH_2CH_2$	80	90:10	44
$c\text{-}C_6H_{11}$	32	85:15	68
$4\text{-}MeOC_6H_4CH_2$	77	99:1	83

Scheme 30

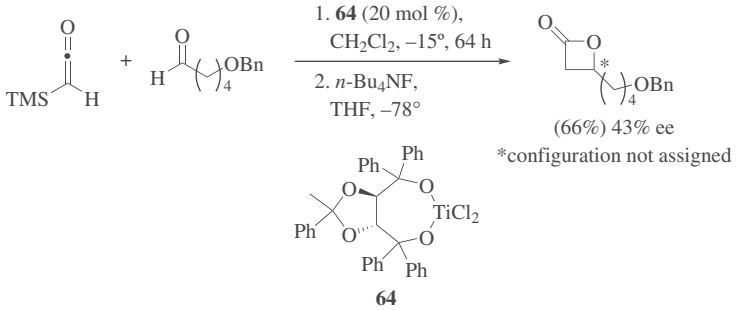
Similar aldehyde-dependent variability in reaction enantioselection is observed for trimethylsilylketene-aldehyde cycloadditions utilizing the menthol-derived Al(III) complex **62** as the catalyst (Scheme 31).[101] Reaction trends parallel those documented for the Al(III)–bis(sulfonamide)-catalyzed reactions, with the trimethylsilylketene-aldehyde cycloadditions being characterized by high

diastereoselectivity and generally modest enantioselectivity except for pentanal (85% ee) and cyclohexanecarboxaldehyde (84% ee). Whereas diastereoselectivity is assayed for the initial α-trimethylsilyl β-lactone cycloadduct **63**, reaction products are characterized as the 4-substituted-2-oxetanones derived from desilylation of the crude cycloadducts.



Scheme 31

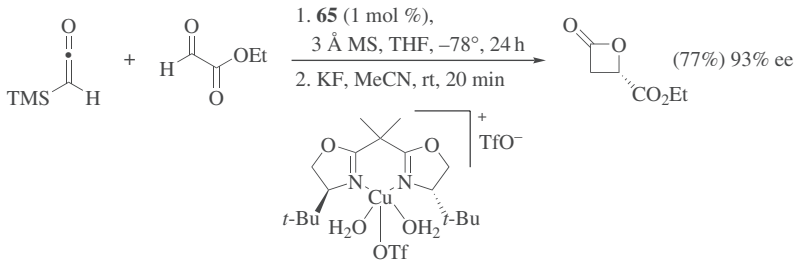
Ti(IV)-Catalyzed Reactions Involving Trialkylsilylketenes. In addition to main-group Lewis acids, several transition-metal-based Lewis acids have been developed for catalytic asymmetric cycloadditions of trimethylsilylketene and aldehyde or activated ketone partners. Adding trimethylsilylketene to solutions of Ti(IV)-TADDOL complex **64** (20 mol %) and various aldehydes affords the *cis*-disubstituted 3-trimethylsilyl-2-oxetanones with high *cis*-diastereoselection (*cis*/*trans* ≥95:5). Reacting the crude β-lactones with fluoride ion effects desilylation to deliver the corresponding 4-substituted 2-oxetanones with good yields and generally modest enantioselectivities (9–80% ee) as illistrated in Eq. 14.[102]



(Eq. 14)

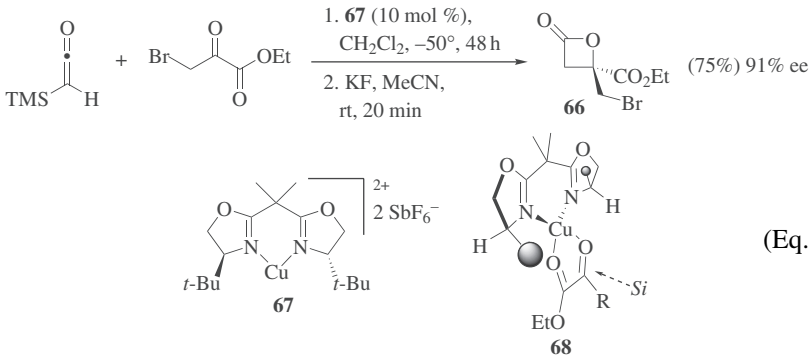
Cu(II)-Catalyzed Reactions Involving Trimethylsilylketene. The conformational mobility available to monodentate Lewis acid–aldehyde complexes often compromises the ability of the chiral catalyst to influence the incipient bond construction, a fact highlighted by the preceding investigations. Limiting the number of conformations available to Lewis acid–Lewis base complexes using multi-point coordination provides a useful strategy for simplifying catalyst design and analysis and, ultimately, enhancing catalyst-based stereocontrol. Copper(II)–bis(oxazoline) Lewis acids make remarkably effective use of this design

wherein high enantioselectivities are achieved in a wide variety of transformations, including carbonyl additions, provided that the substrates are capable of two point binding.[103] Accordingly, Cu(II)–bis(oxazoline) **65** (1 mol %) catalyzes the cycloaddition of trimethylsilylketene with ethyl glyoxylate as the cycloaddition partner to afford the β-lactone with high enantioselection (Eq. 15).[104]

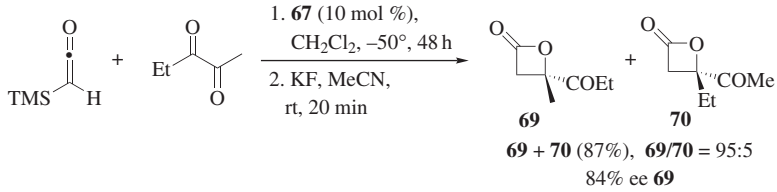


(Eq. 15)

Ketones generally lack sufficient electrophilicity to participate in catalyzed [2 + 2] cycloadditions with ketenes. However, the enhanced electrophilicity of α-dicarbonyl substrates allows the highly enantioenriched 4,4-disubstituted 2-oxetanone **66** to be obtained from trimethylsilylketene cycloadditions using Cu(II)–bis(oxazoline) **67** as the catalyst (83–95% ee) (Eq. 16).[104] Enantioselection for the Cu(II)-catalyzed cycloadditions of α-dicarbonyl substrates is consistent with the distorted square-planar Cu(II)–bis(oxazoline)–α-diketone complex **68** undergoing ketene addition to the exposed *Si* ketone π-face. These same Cu(II)-catalyzed trimethylsilylketene–ketone cycloadditions proceed with high chemoselectivity for the sterically less-encumbered ketone residue in α-diketone substrates to deliver, after desilylation, the enantioenriched β,β-disubstituted β-lactone **69** contaminated with only minor amounts of the isomeric β-lactone **70** (Eq. 17).[104]



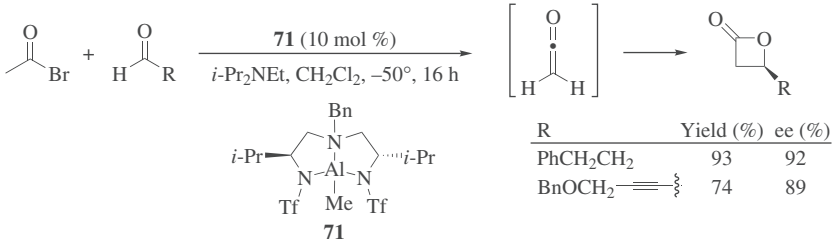
(Eq. 16)



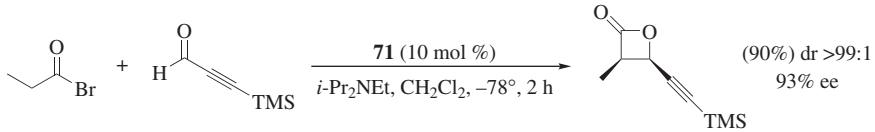
(Eq. 17)

Al(III)-Catalyzed Acyl Halide–Aldehyde Cyclocondensations. The preceding discussion serves to highlight the considerable interest in accessing enantioenriched β-lactones via the ketene cycloaddition pathway. Equally evident, however, are the substantial limitations associated with each of the catalyst systems discussed thus far. The absence of a catalyst system affording uniformly high stereoselectivities in reactions free of severe substrate limitations and requirements for pregenerated ketenes limit the scope of the foregoing methods. The development of Lewis acid catalyzed acyl halide–aldehyde cyclocondensations addresses many of these limitations in providing a general, asymmetric catalytic route to enantioenriched β-lactones.[105]

Acyl halide–aldehyde cyclocondensation (AAC) reactions were developed as a means of realizing highly enantioselective Lewis acid catalyzed cycloadditions of structurally diverse aldehyde partners that incorporate the operational advantages of in situ ketene generation.[106,107] The enantioenriched Al(III)–triamine complex **71** allows the in situ generation of ketenes from acyl bromides to be merged with [2 + 2] cycloadditions with aldehydes to afford the corresponding 4-substituted-2-oxetanones with high enantioselectivity (89–98% ee) (Scheme 32).[105] Using acetyl bromide as the ketene precursor, catalyst **71** engages a variety of enolizable aliphatic as well as aromatic and propargylic aldehydes in highly enantioselective cycloadditions. Analogous cycloadditions of alkyl-substituted ketenes using complex **71** as catalyst are limited to relatively activated aldehyde partners, including aryl and propargyl aldehydes (90–98% ee) (Eq. 18).[108] Nonetheless, cycloadditions of substituted ketenes, generated by in situ dehydrohalogenation of the requisite acyl bromide, affords the 3,4-*cis*-disubstituted β-lactones with excellent relative and absolute stereocontrol.

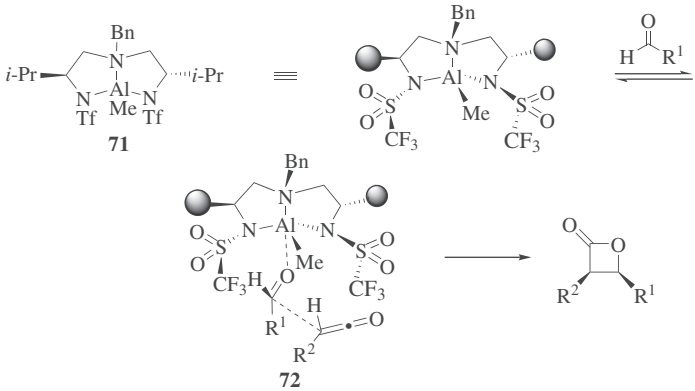


Scheme 32



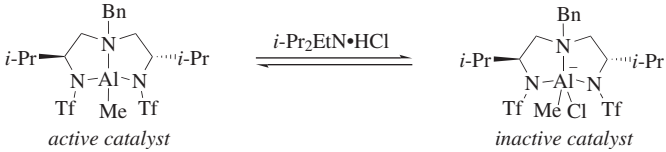
(Eq. 18)

An X-ray crystal structure of complex **71** bound to dimethylformamide provides a model for rationalizing enantioselectivity in the Al(III)-catalyzed acyl halide–aldehyde cyclocondensations (Scheme 33).[109] The carbonyl-bound catalyst **72** adopts a distorted trigonal bipyramidal geometry with the carbonyl Lewis base occupying an apical position. In this orientation, the *N*-sulfonyl moieties on the ligand are ideally situated to differentiate the diastereotopic π bond faces of the aldehyde. Thus, the (*S*,*S*)-catalyst **71** affords a reactive Lewis acid–base complex in which the *Re* face of the aldehyde is exposed to ketene to afford the (4*S*)-β-lactone cycloadduct.



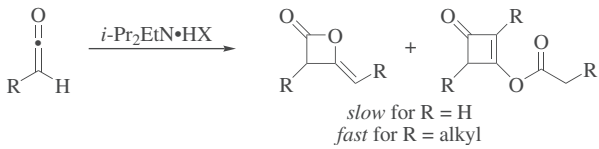
Scheme 33

The Brønsted base required for ketene formation (i-Pr_2Etn) is sufficiently hindered that neither *N*-acylation by the acid halide nor amine coordination to the aluminum-based catalyst compromise the reaction.[110] Control experiments also verify that the trialkylammonium bromide byproduct of ketene generation does not poison the catalyst through halide ion association with the metal center. This observation provides some insight into the requirement for acid bromide ketene precursors in these reactions as it suggests that chloride ion derived from acid chlorides does lead to catalyst poisoning (Eq. 19).[105,108]



(Eq. 19)

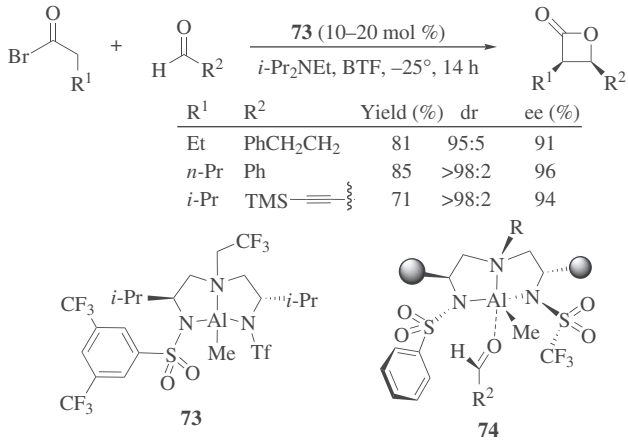
The mechanistic complexity of the acyl halide–aldehyde cyclocondensations necessitates modifications to the original reaction design to successfully engage alkyl-substituted ketenes. Although the trialkylammonium bromide generated in the course of the AAC reactions does not cause catalyst deactivation, it does have a significant impact on the rate of ketene oligomerization. For the ketene generated from acetyl bromide, the catalyzed cyclization reactions of ketene and aldehydes is fast relative to thermal ketene dimerization and trimerization processes. However, for alkyl-substituted ketenes, the trialkylammonium bromide salts accelerate ketene oligomerization so that it kinetically dominates the desired ketene–aldehyde cyclization reaction (Scheme 34).[111] Reestablishing ketene–aldehyde cyclization as the dominant process for substituted ketenes requires salt-free reaction conditions that limit competing ketene oligomerization.



Scheme 34

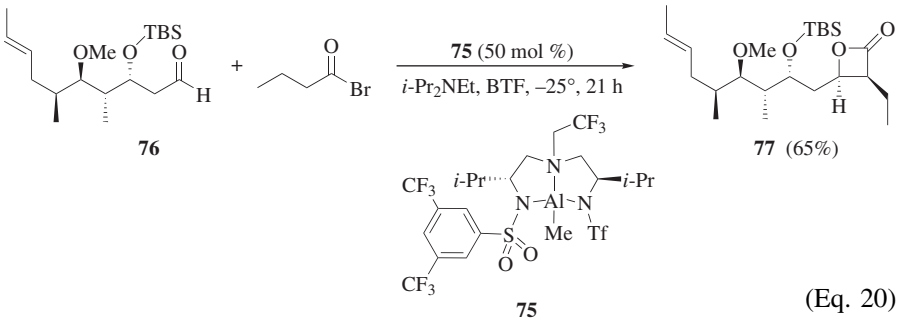
Pseudo salt-free conditions for the AAC reactions are achieved using benzotrifluoride as a replacement for CH_2Cl_2 as solvent.[112] Using benzotrifluoride (BTF) as the reaction solvent, the trialkylammonium bromide byproduct of ketene generation precipitates from the reaction solution. However, at the higher reaction temperatures dictated by the BTF melting point (−29°), the Al(III)–triamine catalyst **71** confers low enantioselectivity. A second generation catalyst **73** derived from an unsymmetrical triamine ligand in conjunction with the BTF solvent affords high enantioselectivities for AAC reactions for a variety of alkyl-substituted ketenes, generated in situ from the corresponding acid bromides, and structurally diverse aldehyde electrophiles (Scheme 35).[112] Design of the second-generation AAC catalyst **73** was predicated on the premise that the trifluoromethanesulfonamide-terminated catalyst **71** affords insufficient facial discrimination to the bound aldehyde substrate at the reaction temperatures dictated by the BTF reaction solvent. An X-ray diffraction analysis of **73** confirms that the aryl sulfonamide adopts a conformation (**74**) wherein the arene ring is ideally positioned to shield the *Si* face of the bound aldehyde.

An asymmetric total synthesis of (−)-pironetin provides an example of the second-generation AAC reaction's applicability to structurally complex aldehyde substrates (Eq. 20).[75] Complex **75** (50 mol %) catalyzes the cyclocondensation of enantioenriched aldehyde **76** with butyryl bromide to generate the *cis*-disubstituted β-lactone **77** as a single diastereomer (65%). Despite the high catalyst loadings required to realize an efficient reaction, this transformation represents a rare example of a catalytic asymmetric butanoate aldol reaction equivalent.[113]



R^1	R^2	Yield (%)	dr	ee (%)
Et	$PhCH_2CH_2$	81	95:5	91
n-Pr	Ph	85	>98:2	96
i-Pr	TMS—≡—⁞	71	>98:2	94

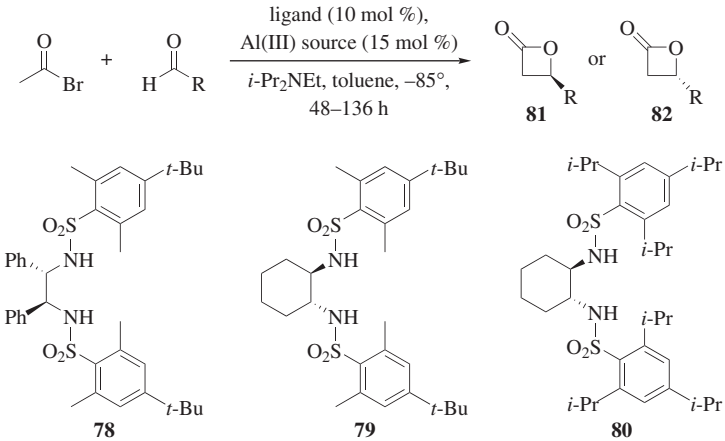
Scheme 35



(Eq. 20)

Bidentate Al(III)–bis(sulfonamide) complexes are also effective catalysts for acetyl bromide–aldehyde cyclocondensation reactions (Scheme 36).[114] The complexes formed by reacting the bis(sulfonamide) ligands **78**–**80** (10 mol %) with either triethylaluminum or diisobutylaluminum hydride (15 mol %) afford reasonably high enantioselectivities for the reactions of acetyl bromide with aliphatic aldehydes to give the β-lactones **81** or **82**. Reaction efficiency exhibits a marked dependence on both ligand structure and ligand–metal stoichiometry. Catalysts incorporating the 1,2-diphenyl-1,2-ethylenediamine ligand **78** afford the highest enantioselectivities for α-branched aldehydes whereas the ligands derived from cyclohexane-1,2-diamine, **79** and **80**, are optimal for linear aldehydes. Moreover, reaction efficiency is maximized for catalysts derived from a 50% excess of triethylaluminum relative to ligand (15 mol % Et_3Al/10 mol % ligand); catalysts obtained from equimolar amounts of triethylaluminum and ligand deliver inferior conversion and enantioselectivity. A related observation regarding aluminum Lewis acid stoichiometry and reaction efficiency was made in the

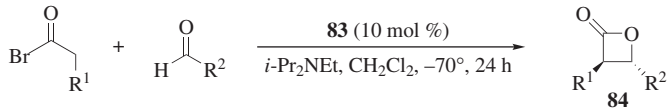
context of diastereoselective Diels–Alder cycloadditions of enantioenriched *N*-acyl oxazolidinones.[115] The optimal diastereoselection achieved in these cycloadditions using excess diethylaluminum chloride (1.4 equiv) was attributed to conformational rigidification achieved upon forming the cationic Al(III)–imide complex wherein the excess Al(III) reagent serves as the halide abstractor. This precedent may suggest that the active Al(III)–bis(sulfonamide) catalysts obtained under these reaction conditions may have some cationic character derived from association, or reaction, with uncomplexed Al(III) reagent.



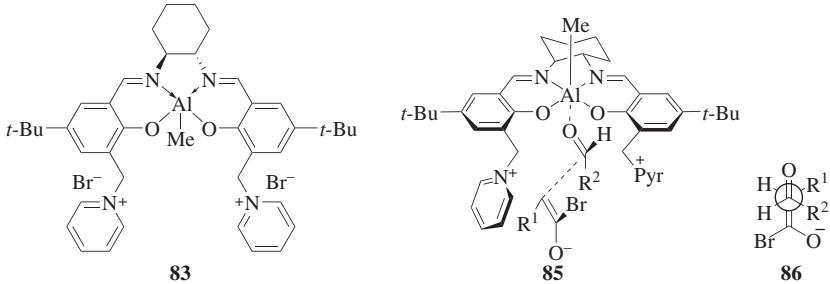
Ligand	Al(III) Source	R	Product	Yield (%)	ee (%)
78	*i*-Bu_2AlH	$PhCH_2CH_2$	**82**	66	82
80	*i*-Bu_2AlH	$PhCH_2CH_2$	**81**	93	88
78	Et_3Al	Et_2CH	**82**	94	80
79	Et_3Al	Et_2CH	**81**	87	68

Scheme 36

Mechanistically distinct acyl bromide–aldehyde cyclocondensations are accessed using the Al(III)–salen catalyst **83** that incorporates pyridinium ion substituents (Scheme 37).[116] Using **83** as catalyst (10 mol %), substituted ketene–aldehyde cycloadditions reverse the typical relative stereochemical bias exhibited by these reactions to deliver *trans*-disubstituted β-lactones **84** with high enantioselectivity (87–94% ee). Pyridinium ion containing catalysts are critical to the success of these reactions as catalysts incorporating uncharged alkyl substituents at these positions afford poor yields of the β-lactones enriched in the typical *cis*-diastereomer. On the basis of this observation, the formal cycloadditions are proposed to proceed through the acid bromide enolate, rather than free ketene, with ion pairing between the enolate and pendant pyridinium salts in the transition state **85** being the determinant factor in defining facial selectivity. Enolate-aldehyde addition via the open transition state **86**, leads, ultimately, to the *trans*-diastereoselection characteristic of these reactions.



R^1	R^2	Yield (%)	dr	ee (%)
Me	n-C_7H_{15}	77	96:4	87
n-Pr	i-Bu	76	96:4	94

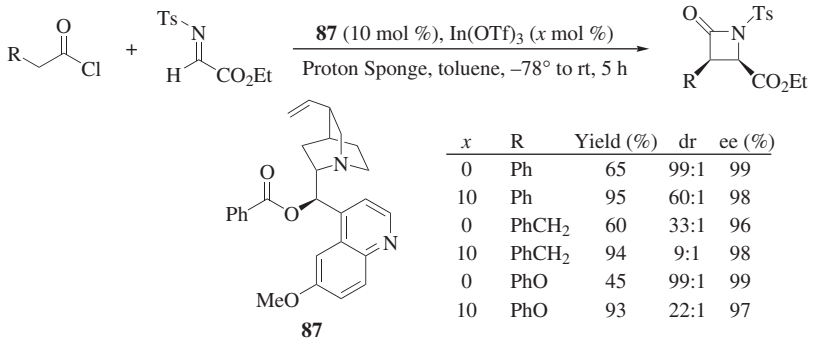


Scheme 37

Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloadditions

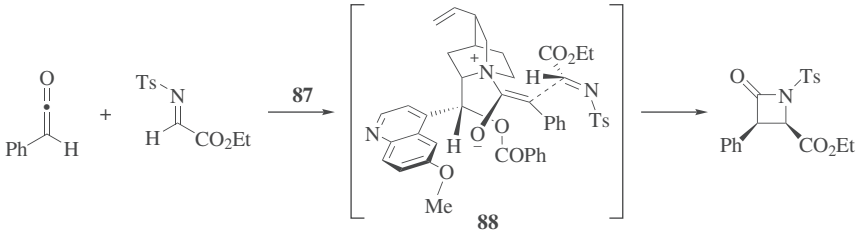
***Cinchona* Alkaloid Catalysts.** Wynberg's discovery that quinidine is a uniquely effective catalyst for asymmetric ketene–aldehyde cycloadditions suggested the use of *cinchona* alkaloids to develop the analogous catalytic, asymmetric ketene–imine cycloadditions.[8,117] In particular, *O*-benzoylquinine (**87**) and *O*-benzoylquinidine are highly effective catalysts for the asymmetric cycloaddition of in-situ-generated ketenes and *N*-tosyl α-imino esters, affording 4-carboalkoxy-2-azetidinones with near perfect absolute and relative stereocontrol (95–99% ee) (Scheme 38).[66,118,119] The α-imino ester substrates are representative of the highly electrophilic, non-enolizable imines that are necessary for effective reactions in these Lewis base catalyzed ketene–imine cycloadditions. The ketene–glyoximine cycloadditions accommodate a range of substitution in the ketene reaction partner, leading to a versatile synthesis of enantioenriched aspartic acid derivatives. The observed sense of enantioselection is consistent with the reaction proceeding via the enantioenriched zwitterionic enolate ensemble **88** that closely resembles the model for stereoinduction originally proposed by Wynberg and supported by computer modeling (Scheme 39).[66] Approach of the imine electrophiles in an *anti*-orientation relative to the enolate with the ester moiety situated to minimize developing non-bonded interactions with the enolate C1 substituent leads to the observed *cis*-diastereoselection.

Yields for these ketene–α-imino ester cycloadditions are improved considerably by including a Lewis acid co-catalyst. Thus, addition of $In(OTf)_3$ (10 mol %) improves reaction yields from 50–60% to consistently above 90% although with a slightly eroded *cis*-diastereoselection (see Scheme 38).[119] It is likely that both mechanisms for ketene cycloaddition catalysis are operative here with Lewis acid mediated imine activation complementing alkaloid-derived ketene activation.[120]



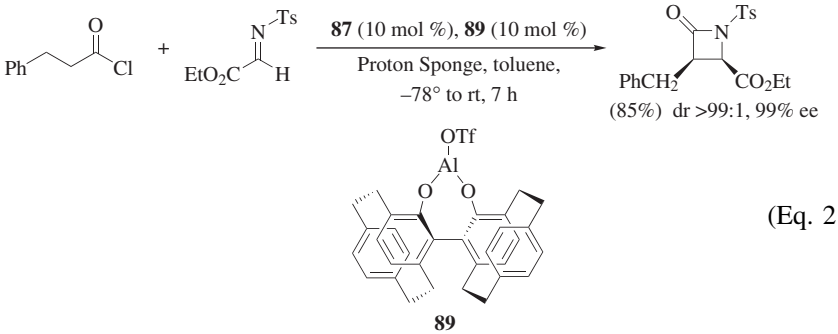
x	R	Yield (%)	dr	ee (%)
0	Ph	65	99:1	99
10	Ph	95	60:1	98
0	$PhCH_2$	60	33:1	96
10	$PhCH_2$	94	9:1	98
0	PhO	45	99:1	99
10	PhO	93	22:1	97

Scheme 38



Scheme 39

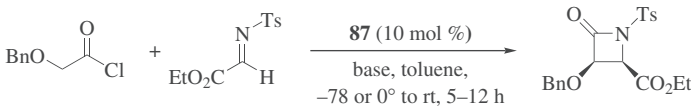
In one trial, the enantioenriched aluminum catalyst **89** bearing a C_2-symmetric bis(cyclophane) ligand functions similarly as a reaction co-catalyst while improving diastereoselection relative to reactions using only Lewis base catalysis or the Lewis base–achiral Lewis acid co-catalyst system (Eq. 21).[121]

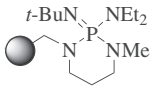


(Eq. 21)

The basic conditions used for in situ ketene generation in the ketene–glyoximine cycloadditions have a measurable effect on reaction efficiency. Thus,

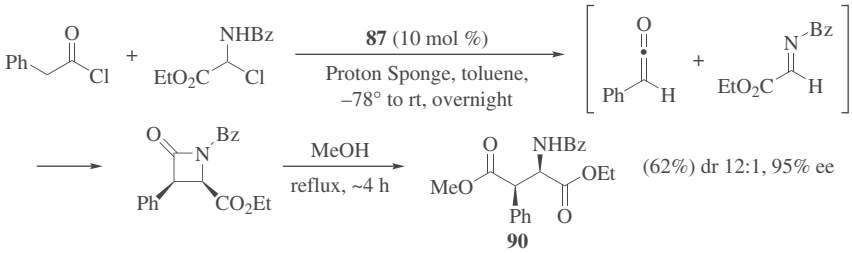
Proton Sponge, NaH/15-crown-5, K_2CO_3, and *N*-phenyl-tris(dimethylamino) iminophosphorane (BEMP) are useful bases for generating acyl chloride-derived ketenes under conditions compatible with the cycloaddition reactions (Scheme 40).[66,122] Although Proton Sponge is the most widely utilized base for ketene–α-imino ester cycloadditions, the NaH/15-crown-5 system is an economical substitute, affording little to no loss in reaction efficiency in several applications.



Base	Yield (%)	dr	ee (%)
Proton Sponge	57	99:1	99
NaH, 15-crown-5	60	25:1	99
K_2CO_3	56	8:1	93
	60	99:1	99

Scheme 40

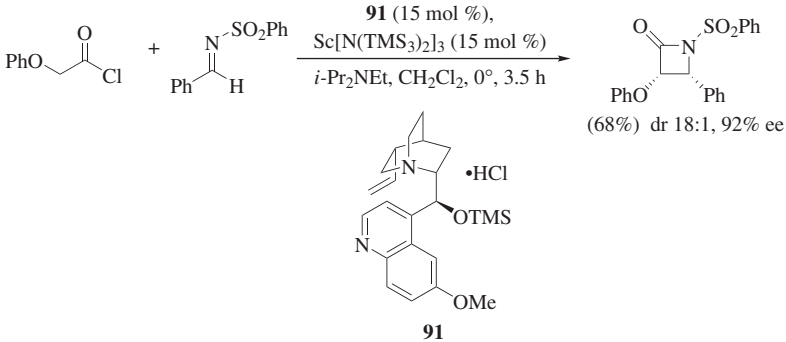
Alkaloid-catalyzed ketene–imine cycloadditions are also used to generate β-lactam cycloadducts that incorporate *N*-acyl protecting groups. For these reactions, *N*-benzoyl-α-chloroglycine serves as the precursor for the requisite α-imino ester via amine-mediated dehydrohalogenation in a process directly analogous to that accessing the ketene reaction partner from the corresponding acyl chloride (Scheme 41).[123,124] The ensuing alkaloid-catalyzed cycloaddition proceeds with enantioselectivity paralleling that observed for the *N*-tosyl imines. The reaction products are isolated as the esters, e.g. **90**, derived from in situ β-lactam ring opening (94–96% ee).



Scheme 41

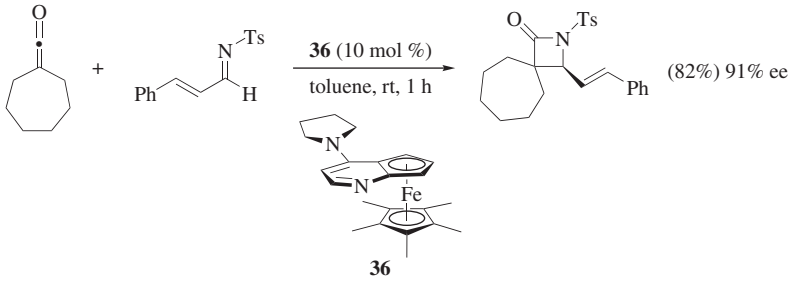
Catalyst systems composed of achiral Lewis acids and *cinchona* alkaloid Lewis bases are also effective as promoters for closely related cycloadditions where less electrophilic aryl aldimines replace α-imino esters in the Staudinger-type cycloadditions (Eq. 22).[125] For these reactions, stereoselectivity is optimized

using *O*-trimethylsilylquinidine (**24**), with the hydrochloride salt **91** serving as the catalyst precursor, in conjunction with $Sc[N(TMS)_2]_3$ (15 mol % each) as the catalyst for the [2 + 2] cycloaddition of *N*-sulfonyl aryl aldimines and in situ generated phenoxyketene. This reaction system delivers the corresponding *cis*-disubstituted β-lactams with the uniformly high enantioselectivities that characterize the alkaloid-catalyzed [2 + 2] cycloadditions. Cycloaddition diastereoselection exhibits a marked dependence on Lewis acid structure with *cis*-diastereoselection maximized for the sterically large lanthanide tris(hexamethyldisilazide) Lewis acids. The utility of this catalyst system for the synthesis of structurally diverse β-lactam heterocycles is limited, however, as only phenoxyketene and aryl aldimines constitute effective substrates.

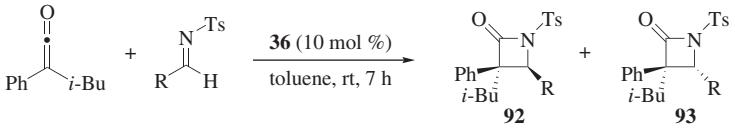


(Eq. 22)

Fe(II)–Azaindene Catalysts. As the mechanistic course of Lewis base catalyzed ketene–imine cycloadditions parallels that of ketene–carbonyl cycloadditions, the discovery of catalysts for these related transformations finds similar parallels. Thus, the Lewis basicity expressed by 4-(pyrrolidino)pyridine complex **36** renders this Fe(II) complex an excellent catalyst for the enantioselective cycloaddition of disubstituted ketenes with nonenolizable *N*-tosyl aldimines. Symmetrical, disubstituted ketenes react with aryl, α,β-unsaturated, and α,α-disubstituted imines using catalyst **36** (10 mol %) to afford the spiro-fused β-lactams with generally high enantiomeric excess (81–94% ee) (Eq. 23).[126] Unsymmetrical disubstituted ketenes react similarly with *N*-tosyl aldimines producing the trisubstituted β-lactams **92** with excellent absolute stereocontrol and only minor quantities of the diastereomeric cycloadduct **93** (89–98% ee, dr = 89:11–94:6) (Scheme 42).[126] As with the Fe(II)–azaindene-catalyzed ketene–aldehyde cycloadditions, these reactions are distinct from their alkaloid-catalyzed counterparts in that only the azaindene catalyst engages disubstituted ketenes as effective cycloaddition partners and, therefore, affords privileged access to quaternary carbon stereocenters via the ketene cycloaddition pathway.



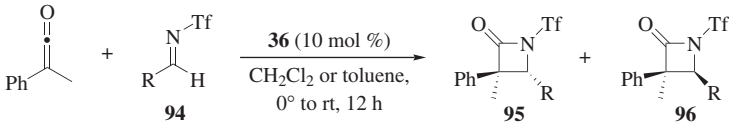
(Eq. 23)



R	92 + 93 Yield (%)	92/93	ee (%) 92
2-furyl	97	11:1	98
c-C_3H_5	88	15:1	89

Scheme 42

The imine nitrogen activating group plays a significant role in defining the stereoselectivity of the Fe(II)-catalyzed ketene–imine cycloadditions. While *N*-tosyl imines afford the *cis*-disubstituted β-lactams as the major diastereomer, imines possessing *N*-triflyl groups yield the *trans*-β-lactams as the predominant diastereomers (Scheme 43).[127] Thus, reacting alkyl aryl ketenes with *N*-triflyl aldimines **94** using the Fe(II)–5-azaindene complex **36** as the catalyst provides the trisubstituted β-lactams **95** and **96** with high enantioselectivity but with diastereoselectivity reversed relative to that observed for the corresponding *N*-tosyl aldimine substrates.

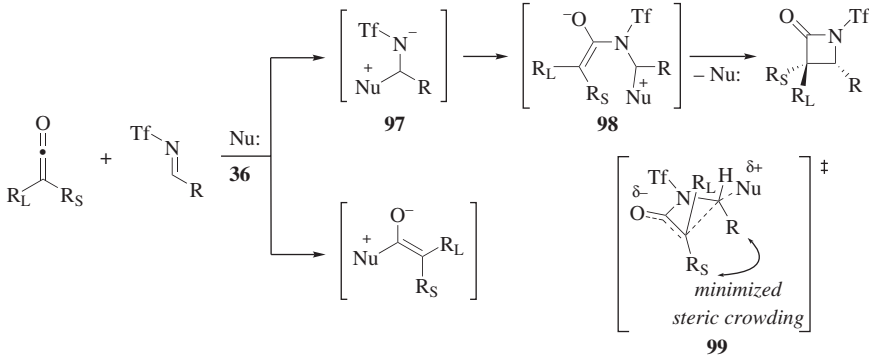


R	95 + 96 Yield (%)	95/96	ee (%) 95
Ph	83	98:2	81
4-$MeOC_6H_4$	76	81:19	82

Scheme 43

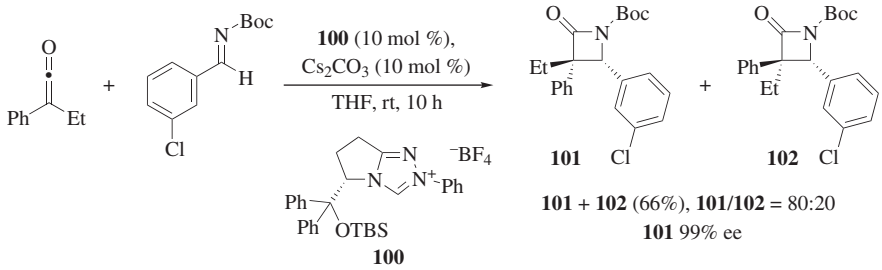
The enhanced electrophilicity of the *N*-triflyl imines is believed responsible for this turnover in diastereoselection, providing access to a reaction mechanism deviating from the conventional zwitterionic enolate-dependent pathway

(Scheme 44).[127] Typically, the ketene reaction components possess greater electrophilicity relative to the imine substrates and, thus, react preferentially with the Lewis basic catalyst ("Nu:" in Scheme 44) to access the ammonium ion enolate reaction pathway. However, *N*-triflyl aldimines offer sufficient electrophilicity that the base-catalyzed cycloaddition is initiated by Lewis base (catalyst) addition to the imine to afford zwitterion **97**.[48,128] The triflamide anion then serves as the nucleophile during addition to ketenes to afford the zwitterionic enolate **98**. An ensuing intramolecular substitution affords the β-lactam product with concomitant catalyst regeneration. Minimization of developing eclipsing interactions during the annulation event (e.g., **99**) is, apparently, responsible for the "*trans*" diastereoselection observed for these reactions.

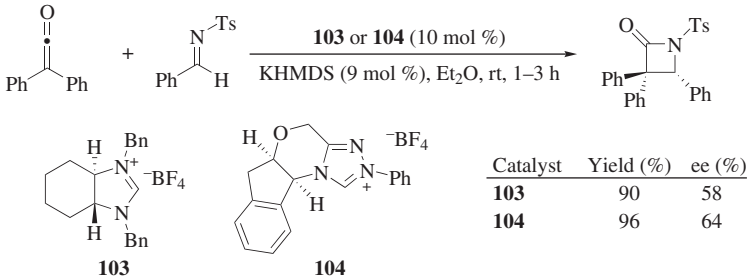


Scheme 44

Heterocyclic Carbene Catalysts. The ability of *N*-heterocyclic carbenes to access the requisite zwitterionic enolate intermediates upon addition to ketenes renders them candidates as Lewis basic catalysts for ketene–imine cycloadditions. Indeed, various enantioenriched heterocyclic carbenes have found utility as catalysts for asymmetric cycloadditions of nonenolizable aryl imines with pregenerated disubstituted ketenes. The carbene derived from triazolium salt **100** engages unsymmetrically disubstituted ketenes in analogous cycloadditions with aryl *N*-Boc aldimines to afford *cis*-3,3,4-trisubstituted β-lactams, e.g. **101**, with high enantioselection (91–99% ee), albeit with generally modest diastereoselection (**101/102** = 2.4:1–99:1) (Eq. 24).[129] These reactions offer the relatively rare example of catalyzed Staudinger cycloadditions of imines possessing carbamate protecting groups on nitrogen rather than the far more common sulfonyl-derived protecting groups. The latter is, again, exemplified in reactions utilizing the imidazole- and 1,2,4-triazole-based carbenes generated in situ from the corresponding tetrafluoroborate salts **103** and **104**, respectively, as catalysts for the cycloaddition of diphenylketene with several aryl *N*-tosyl aldimines that deliver the corresponding β-lactams with moderate enantioselectivity (55–75% ee) (Scheme 45).[130]



(Eq. 24)

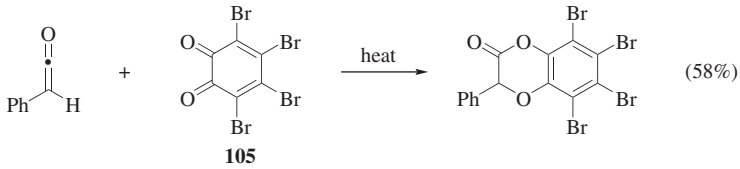


Catalyst	Yield (%)	ee (%)
103	90	58
104	96	64

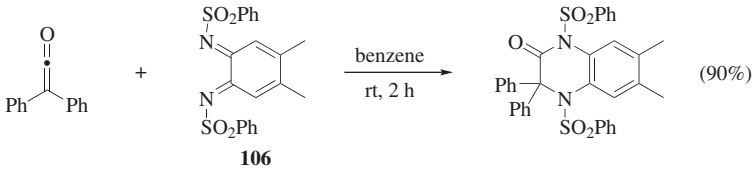
Scheme 45

[4 + 2] Cycloadditions: Ketene Dienophiles

***o*-Benzoquinone and *o*-Benzoquinone Imine Dienes.** *o*-Benzoquinones express nucleophile-dependent reactivity as electrophiles driven by the aromatization that accompanies nucleophilic attack on oxygen.[131] Ketenes are among the nucleophiles adding at oxygen wherein the nascent negative charge engendered at the phenolic oxygen and the accompanying increased positive charge at the carbonyl carbon in the transition state are ideally matched, thus eliciting a formal [4 + 2] cycloaddition. Indeed, tetrahalo *o*-benzoquinones, for example *o*-bromanil (**105**), constitute a family of heterodienes that participate in thermal, net [4 + 2] cycloadditions with phenylketene to afford benzodioxin-2-one (Eq. 25).[132] The electronic homology existing between *o*-quinones and the corresponding *o*-benzoquinone diimines such as **106** is manifest in similar reactivity with ketenes. Thus, the thermal cycloaddition of diarylketenes with *N*,*N*′-((1*E*,2*E*)-4,5-dimethylcyclohexa-3,5-diene-1,2-diylidene)dibenzenesulfonamide (**106**) affords dihydroquinoxalin-2-one from the [4 + 2] cycloaddition (Eq. 26).[133]

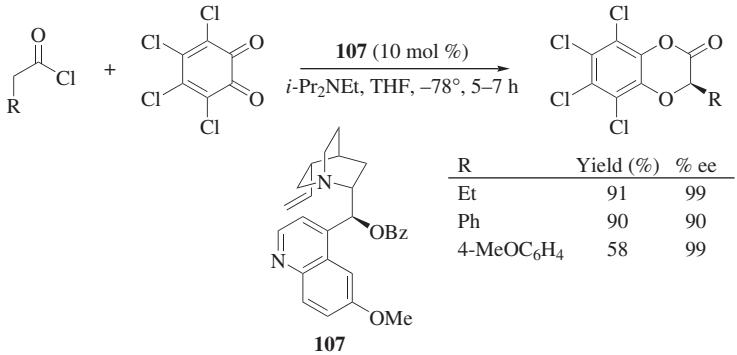


(Eq. 25)



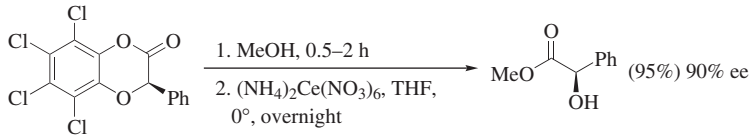
(Eq. 26)

The reliance of these reactivity patterns on the nucleophilic properties of ketenes suggests that Lewis basic addends that enhance intrinsic ketene nucleophilicity should function as catalysts for these reactions.[14] Indeed, in situ generated ketenes add to *o*-chloranil using *O*-benzoylquinidine (**107**) as the catalyst to afford highly enantioenriched benzodioxin-2-ones as formal [4 + 2] cycloadducts (Scheme 46).[134] Both alkyl and aryl ketenes, generated in situ from the corresponding acid chlorides, provide the enantioenriched benzodioxanes with very high enantioselectivity. The identity of the enantioenriched benzodioxanes as precursors to structurally diverse α-hydroxy esters is revealed by transesterification of the lactone linkage and oxidative cleavage of the resulting aryl ether (Eq. 27).[134]



R	Yield (%)	% ee
Et	91	99
Ph	90	90
4-MeOC$_6$H$_4$	58	99

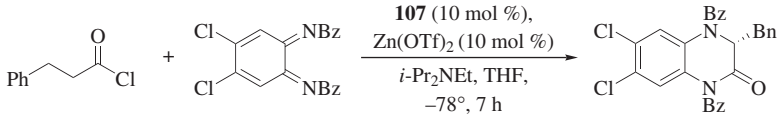
Scheme 46



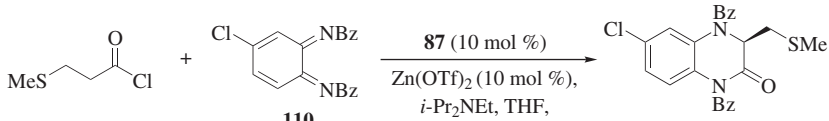
(Eq. 27)

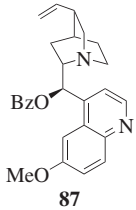
N,*N*′-(4,5-Dichlorocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (**108**) functions similarly to *o*-chloranil in alkaloid-catalyzed ketene cycloadditions to provide highly enantioenriched dihydroquinoxalin-2-one cycloadducts, e.g. **109** (Eq. 28).[135] The formal [4 + 2] cycloadditions involving the bisimine dienes require $Zn(OTf)_2$ as a Lewis acid co-catalyst, presumably to enhance the electrophilicity of the diene component. Alkaloid-catalyzed cycloaddition of monosubstituted ketenes to the unsymmetrical 4-chloro bisimine **110** occurs with

enolate addition to the imine moiety proximate to the halogen substituent, yielding the monohalogenated dihydroquinoxalin-2-one derivative with high regio- and enantioselectivity (Eq. 29).[135]



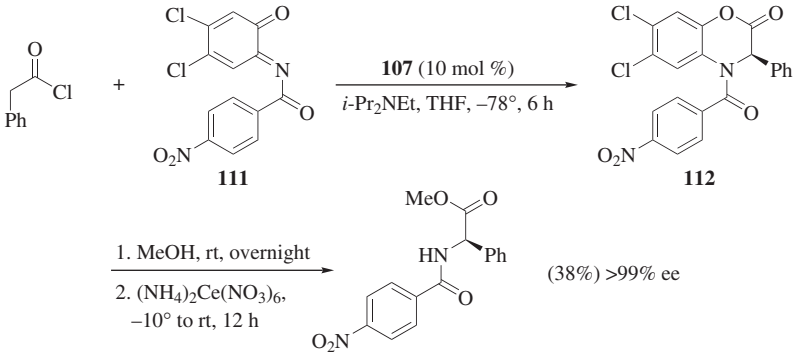
(Eq. 28)





(Eq. 29)

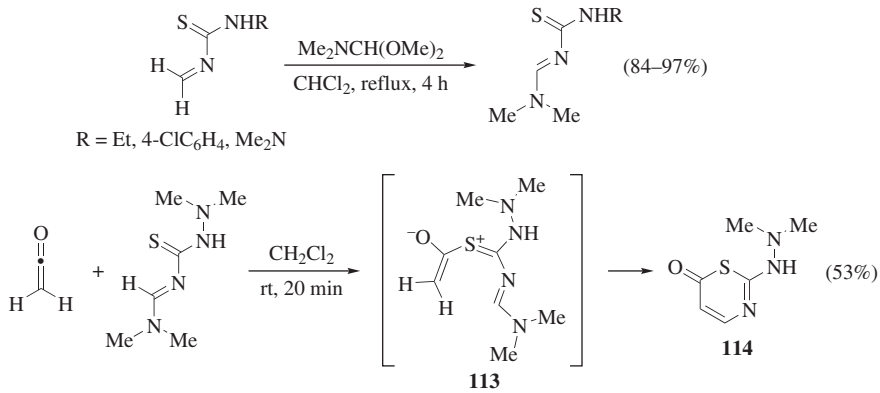
The regiochemical preferences exhibited in the bisimine cycloadditions are also manifest in ketene additions employing unsymmetrical *o*-benzoquinone imine electrophiles as represented by nitrobenzamide **111** (Scheme 47).[136] Suitable derivatization of the *o*-benzoquinone imine nitrogen elicits addition of the ketene-derived enolate at nitrogen to the near exclusion of addition at the quinone oxygen to afford benzooxazin-2-one derivatives such as **112**. Ketene additions to the unsymmetrical *o*-benzoquinone imine share the uniformly high enantioselectivity associated with the *o*-chloranil and bisimine cycloadditions. However,



Scheme 47

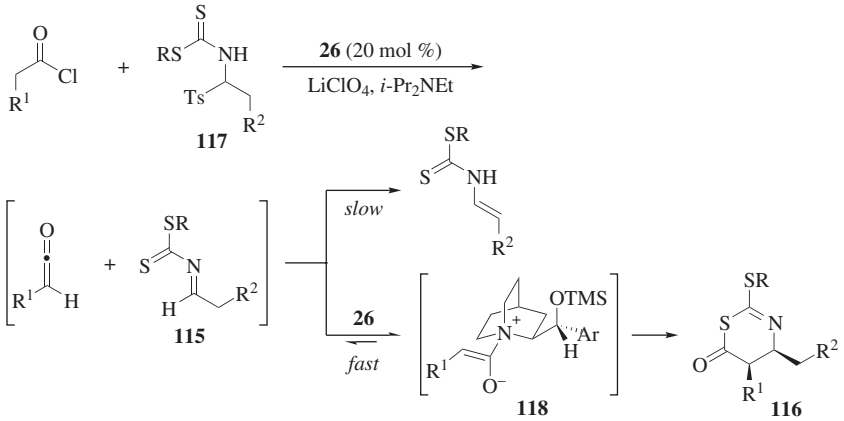
these cycloadducts offer the attractive feature of being readily transformed into enantioenriched α-amino acid derivatives.[137] Thus, alcohol-mediated lactone ring opening and oxidative cleavage of the resulting *N*-aryl amides afford the corresponding α-amido ester derivatives.

Thiocarbamoyl Imine-Derived Dienes. Ketene–imine cycloadditions can be diverted from the prototypical Staudinger-type pathway by suitable derivatization of the imine reaction component. While myriad examples exist of *N*-acyl imines delivering formal [2 + 2] cycloadducts with ketenes, *N*-thioacyl imines undergo thermal cycloadditions with ketenes to afford the products of formal [4 + 2] cycloadditions (Scheme 48).[138] It would appear that sulfur Lewis basicity serves to access the zwitterionic intermediate **113** that, in accord with the mechanism operative in *N*-alkyl imine–ketene Staudinger-type cycloadditions, participates in an electrocyclic ring closure to generate the formal [4 + 2] cycloadduct **114**.



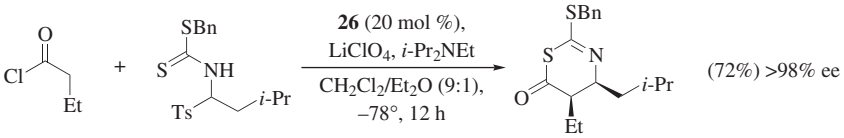
Scheme 48

The propensity of imines possessing *N*-thiocarbonyl moieties to afford formal [4 + 2] cycloadducts is also manifest in Lewis base catalyzed reaction variants. Thus, dithiocarbamate-derived imines **115** react with alkyl-substituted ketenes using *cinchona* alkaloids as catalysts to afford enantioenriched 2,6-thiazinone cycloadducts **116** (Scheme 49).[139] In these reactions, both ketene and imine reaction components are generated in situ by tertiary amine-mediated deprotonation of acid chlorides and α-amido sulfones **117**, respectively.[140] Efforts to render these reactions compatible with aliphatic and, therefore, enolizable imines inspired a reaction design involving in situ imine generation as a mechanism for circumventing competing imine-to-enamine tautomerization.[53] Imine formation is presumed not to be instantaneous under these conditions, thereby allowing reaction of the ketene-derived enolate **118** with low concentrations of imine **115** to minimize the enamine formation that would accompany extended exposure of **115** to the reaction conditions.

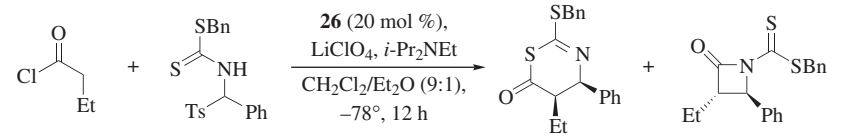


Scheme 49

Catalyst systems for the acyl chloride–α-amido sulfone cyclocondensations are comprised of *O*-silylated *cinchona* alkaloids, required for accessing the ubiquitous acylammonium ion enolate, in conjunction with Li(I) Lewis acids as activators for the electrophilic imine.[139] Under these conditions, a variety of alkyl-substituted ketenes and aliphatic imines deliver 2,6-thiazinone cycloadducts with excellent control of both absolute and relative stereochemistry (Eq. 30).[139] Cycloadditions involving aryl α-amido sulfones afford modestly attenuated yields of thiazinones (e.g., **119**) due to competing formation of the β-lactam adducts (e.g., **120**), possessing the unanticipated *trans*-diastereoselection that is not observed for alkyl imine electrophiles (Eq. 31).[139] In all cases, optimal reaction efficiency is obtained using 20 mol % catalyst loading (**24** or **26**), which presumably increases the cycloaddition reaction rate relative to catalyst-independent imine tautomerization, thereby minimizing formation of the *N*-acylated enamine observed using lower catalyst loadings.



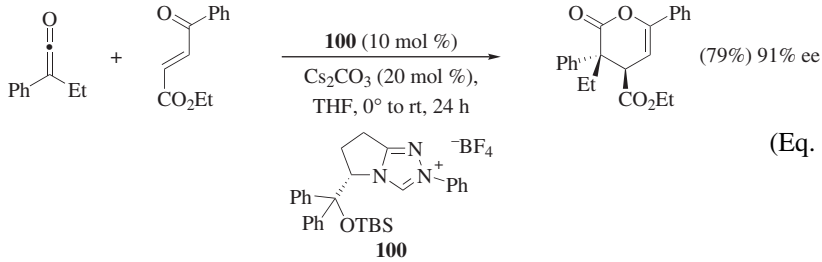
(Eq. 30)



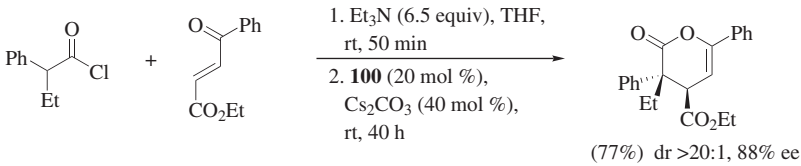
119 + **120** (74%), **119/120** = 80:20
>98% ee **119**

(Eq. 31)

Conjugated Enone Dienes. Vinylogous α-keto esters are another family of highly electrophilic heterodienes that exploit the nucleophilic character of ketenes to arrive at formal [4 + 2] cycloadditions. In this case, enantioenriched triazolium-derived carbenes (e.g., as generated from **100**) serve as catalysts for the reaction of alkyl aryl ketenes with β-aroylacrylates to afford 2-pyranone cycloadducts (Eq. 32).[141] Relative and absolute stereocontrol in these reactions parallel those obtained from the closely related ketene–imine cycloadditions involving the same carbene catalyst. In this instance, the pyrone cycloadducts are obtained with generally high *trans*-diastereoselection and enantioselectivity (84–91% ee, *trans*/*cis* = 15:1 to >99:1). The reaction efficiency for the cycloaddition employing 2-phenylbutanoyl chloride and triethylamine as the ketene source parallels that obtained using pregenerated ethylphenylketene, indicating that these carbene-catalyzed [4 + 2] cycloadditions tolerate in situ ketene generation (Eq. 33).[141] Reactions involving ketene dienophiles and enediones having substituents other than aryl rings at C2 and C4, respectively, are not described.

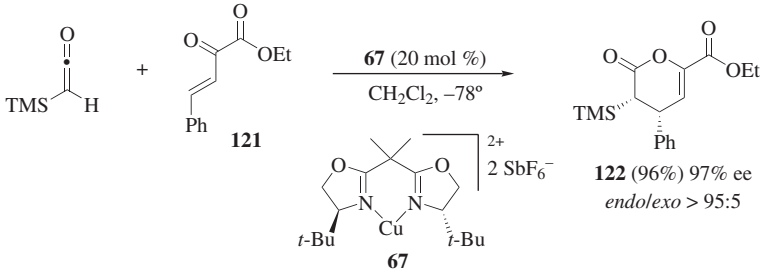


(Eq. 32)



(Eq. 33)

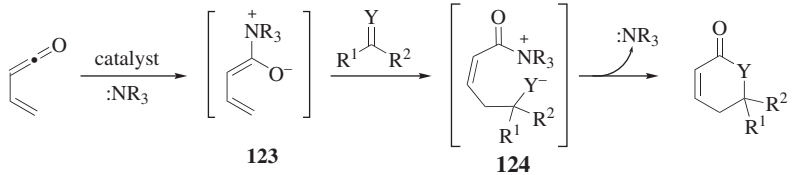
Consistent with the related Cu(II)-catalyzed ketene–glyoxylate [2 + 2] cycloadditions, the Cu(II)-bis(oxazoline) complex **67** catalyzes a hetero-Diels–Alder reaction between trimethylsilylketene and the unsaturated α-keto ester **121** (Eq. 34).[104] In this single example, the δ-lactone cycloadduct **122** is obtained with near perfect enantioselection (97% ee) and *endo*-diastereoselection (>95:5).



(Eq. 34)

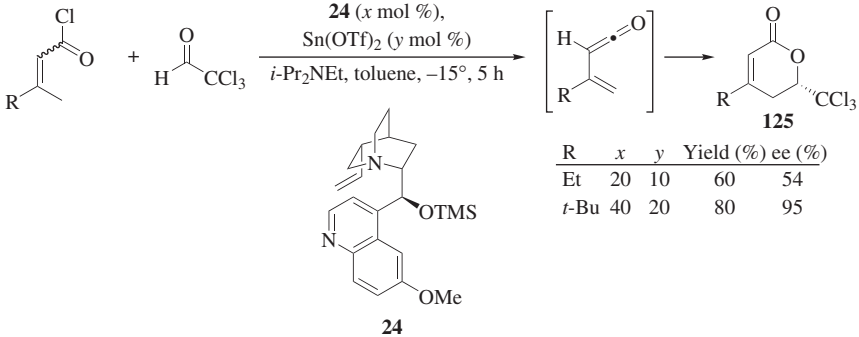
[4 + 2] Cycloadditions: Ketene Dienes

The tendency of vinyl ketenes to undergo thermal pericyclic cascade sequences can be diverted using Lewis base catalysis to arrive at [4 + 2] cycloadducts derived from unsaturated ketenes functioning as extended enolates.[59,142] For example, vinyl ketenes can react with Lewis base catalysts (R_3N) to form the extended enolate **123** (Scheme 50). Ensuing electrophile addition at the γ-position of the enolate affords the vinylogous aldol adduct **124** that, upon lactonization, yields the formal [4 + 2] cycloadduct.



Scheme 50

This reaction design has been implemented in the reaction of 3-substituted crotonyl chlorides with chloral using *O*-trimethylsilylquinidine as the Lewis basic catalyst (20–100 mol %) (Scheme 51).[143] Lewis acidic additives are essential for these transformations, although their role is believed to be as accelerants for acid chloride deprotonation rather than assisting the cycloaddition. Although a number of metal triflates serve in this capacity, the reaction has been optimized using $Sn(OTf)_2$ as the Lewis acid addend, presumably due to cost considerations. The highly electrophilic chloral is the only useful electrophile for these reactions, supporting the supposition that the Lewis acid addend does not function to provide additional activation to the aldehyde dienophile. Enantioselectivities in the [4 + 2] cycloadditions with chloral are optimized for acid chlorides possessing sterically large groups at C3 and afford the derived pyranone cycloadducts **125** in moderate to good yields (58–80%). Reactions involving in-situ-generated vinyl

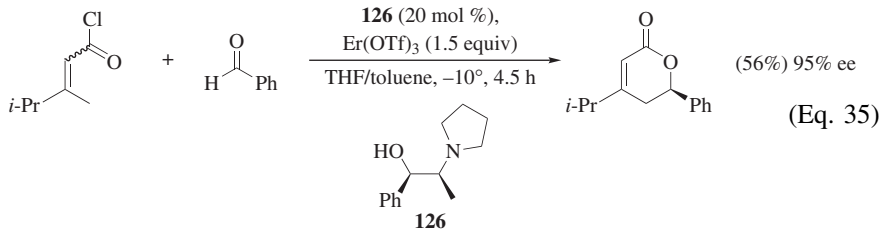


R	x	y	Yield (%)	ee (%)
Et	20	10	60	54
t-Bu	40	20	80	95

Scheme 51

ketenes incorporating trialkylsilyl residues at C3 generally require stoichiometric quantities of the alkaloid promoter for efficient reaction.

These Lewis base catalyzed alkenyl ketene [4 + 2] cycloadditions are extended to aryl aldehyde "dienophiles" by using ephedrine derivative **126** as the catalyst in conjunction with stoichiometric or greater quantities of erbium triflate (Eq. 35).[144] Synthetically useful yields of the 6-aryl-2-pyranone cycloadducts are obtained using amino alcohol **126** as catalyst (10–20 mol %), at the expense of using excess $Er(OTf)_3$ (1.5 equiv) as a promoter. In contrast to the alkaloid-catalyzed variants of these cycloadditions, the Lewis acid promoter is hypothesized to play an active role in mediating the bond construction events. Under these conditions, 3-substituted crotonyl chlorides incorporating both phenyl and alkyl substituents react with various aryl aldehydes to afford the 2-pyranone cycloadducts with high enantioselectivity (88–98% ee). Cycloaddition efficiency correlates with the electronic properties of the aldehyde as reaction yields are enhanced for aldehydes having electron-withdrawing substituents and are reduced for those incorporating electron-rich aryl rings. Aliphatic aldehydes, both enolizable and nonenolizable, are not effective dienophiles under these reaction conditions.



(Eq. 35)

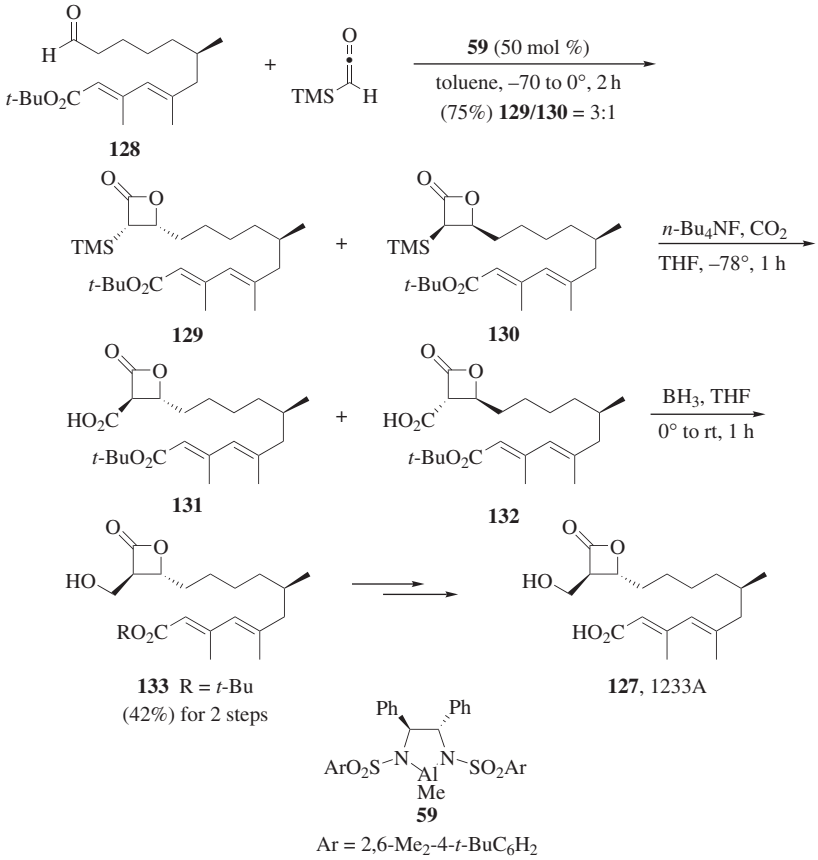
APPLICATIONS TO SYNTHESIS

The efficiency that characterizes β-lactam and β-lactone syntheses via the corresponding ketene cycloadditions logically implicates these transformations as strategic elements in the synthesis of natural products, or other complex targets, that incorporate these heterocycles. It is interesting to note, that although a wide array of β-lactam-containing antibacterial agents represent important targets for total synthesis, the utility of catalytic asymmetric ketene–imine cycloadditions in this context is not extensively documented. Conversely, similarly attractive β-lactone-containing target structures, are relatively rare; nevertheless a comparatively large collection of target-oriented syntheses exist that exploit catalytic asymmetric ketene–carbonyl cycloadditions. The applications of catalytic asymmetric ketene-based cycloadditions to target-oriented syntheses presented here highlight the considerable power of ketene–aldehyde cycloadditions and ketene dimerizations, both as strategic entries to β-lactone-containing target structures and also as highly efficient surrogates for catalytic, asymmetric aldol addition reactions. The logical correlation between enantioenriched β-lactam

chemotherapeutic agents and catalytic asymmetric ketene–imine cycloadditions is also detailed in the context of an enantioselective carbapenem synthesis.

Lewis Base and Lewis Acid Catalyzed [2 + 2] Ketene–Aldehyde Cycloadditions

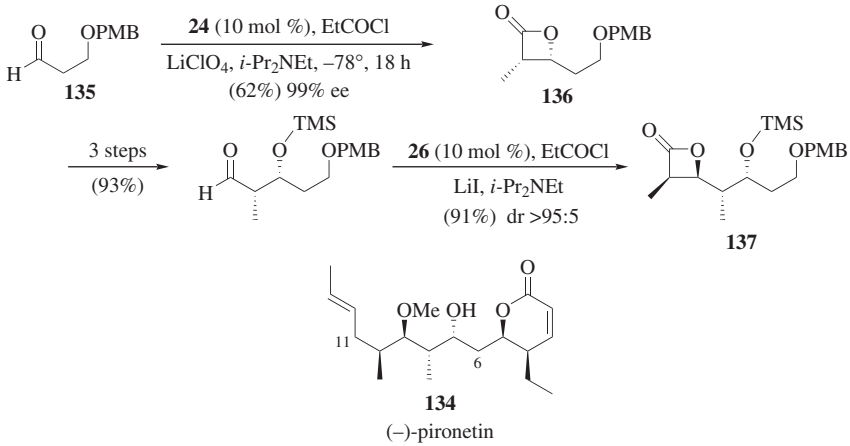
Al(III)-Catalyzed Reactions Involving Trimethylsilylketene. Although the utility of trialkylsilylketene cycloaddition partners derives largely from their relative immunity toward dimerization, the trialkylsilyl substituent present within the derived cycloadduct can be exploited for reaction pathways that are difficult to access using traditional protocols. Specifically, fluoride-mediated desilylation of α-trialkylsilyl β-lactones affords β-lactone enolates that are difficult to access using traditional enolization method because of their proclivity for self-condensation.[145] This reactivity pattern is highlighted in a synthesis of the hypocholesterolemic agent 1233A (**127**) wherein a Lewis acid catalyzed trimethylsilylketene–aldehyde cycloaddition delivers the β-lactone that is characteristic of the target structure (Scheme 52).[99] Thus,



Scheme 52

aldehyde **128** reacts with trimethylsilylketene using the Al(III)–bis(sulfonamide) complex **59** as the catalyst (0.50 equiv) to afford a mixture of diastereomeric *cis*-disubstituted β-lactones **129** and **130**. Reacting the mixture of β-lactones with tetra-*n*-butylammonium fluoride reveals the β-trialkylsilyl β-lactones as masked 2-oxetanone enolates. In situ carboxylation is controlled by the C4 stereocenter to afford the corresponding *trans*-disubstituted 2-oxetanone-3-carboxylic acids **131** and **132**. Borane-mediated reduction of the crude mixture affords the corresponding α-hydroxymethyl-β-lactones from which the major diastereomer **133** is isolated by column chromatography (42% over two steps) and, ultimately, converted into 1233A.

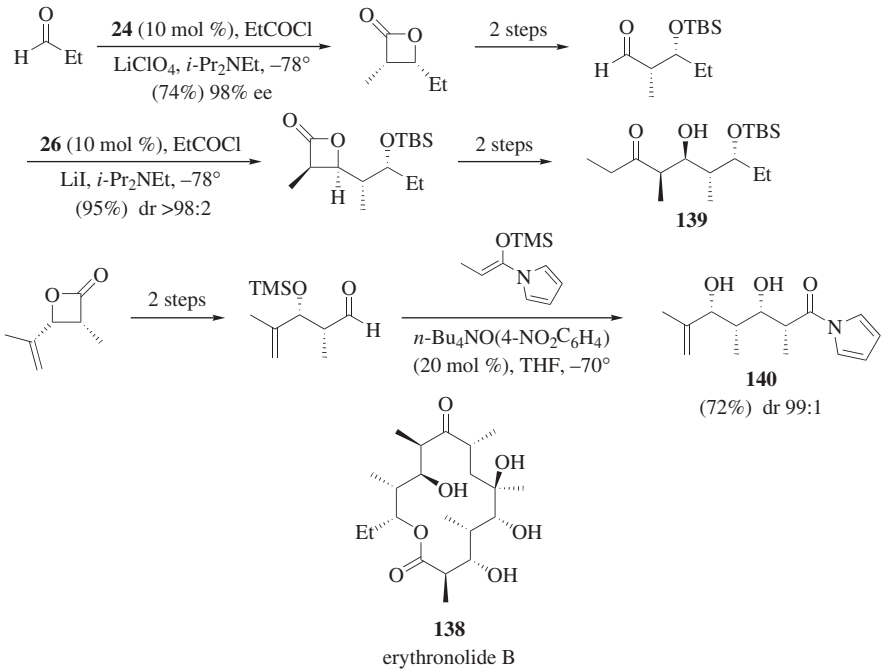
Alkaloid-Catalyzed [2 + 2] Cycloadditions of Unactivated Aldehydes. A strategy for catalytic asymmetric polypropionate construction based on alkaloid-catalyzed ketene–aldehyde cycloadditions is exemplified in an asymmetric total synthesis of the naturally occurring anti-tubulin agent (−)-pironetin (**134**) (Scheme 53).[75] Accordingly, simple catalyst-based stereocontrol in the AAC homologation of aldehyde **135** establishes the C7–C8 *syn*-relationship in generating β-lactone **136**. Ensuing matched double diastereoselective AAC homologation of the aldehyde obtained from **136** delivers the C7–C10 *syn,anti,syn*-β-lactone **137** required for completing the pironetin synthesis. Interestingly, a Lewis acid catalyzed variant of the ketene cycloaddition is used later in the synthesis to introduce the C4 and C5 stereogenic centers.



Scheme 53

Total syntheses of the stereochemically complex polyketides erythronolide B (**138**)[146] and apoptolidinone C (**141**)[147] further illustrate the utility of these catalytic asymmetric ketene–aldehyde cycloadditions. Alkaloid-catalyzed acyl halide–aldehyde cyclocondensations are used to establish the C2–C3, C10–C11,

and C12–C13 propionate aldol relationships present in propionate trimer fragments **139** and **140** used to assemble erythronolide. The remaining four stereocenters present in the erythromycin aglycone are derived indirectly from these catalyzed cycloadditions by diastereoselective transformations (Scheme 54).[146] A synthesis of apoptolidinone C, the aglycone of the potent apoptosis regulator apoptolidin C, further exemplifies the power of catalytic AAC reactions as asymmetric aldol equivalents. In this synthesis, Lewis base catalyzed variants establish the propionate aldol relationships existing at C8–C9, C22–C23 and C24–C25, whereas cyclocondensations catalyzed by the Al(III) complexes **142** and **143** serve as acetate aldol equivalents during installation of the C17 and C27 stereocenters (Fig. 7).[147] Indeed, catalytic asymmetric ketene cycloadditions are directly responsible for establishing eight of the ten stereocenters arrayed about the apoptolidinone aglycone with the remaining two stereocenters being set by diastereoselective transformations exploiting the cycloaddition-derived stereogenic centers.



Scheme 54

***Cinchona* Alkaloid-Catalyzed Ketene Dimerization.** The enantioenriched 4-alkylidene-2-oxetanones obtained from alkaloid-catalyzed alkyl ketene dimerizations represent masked chiral β-keto amide enolates.[148–151] The asymmetric total synthesis of siphonarienedione highlights this method as an

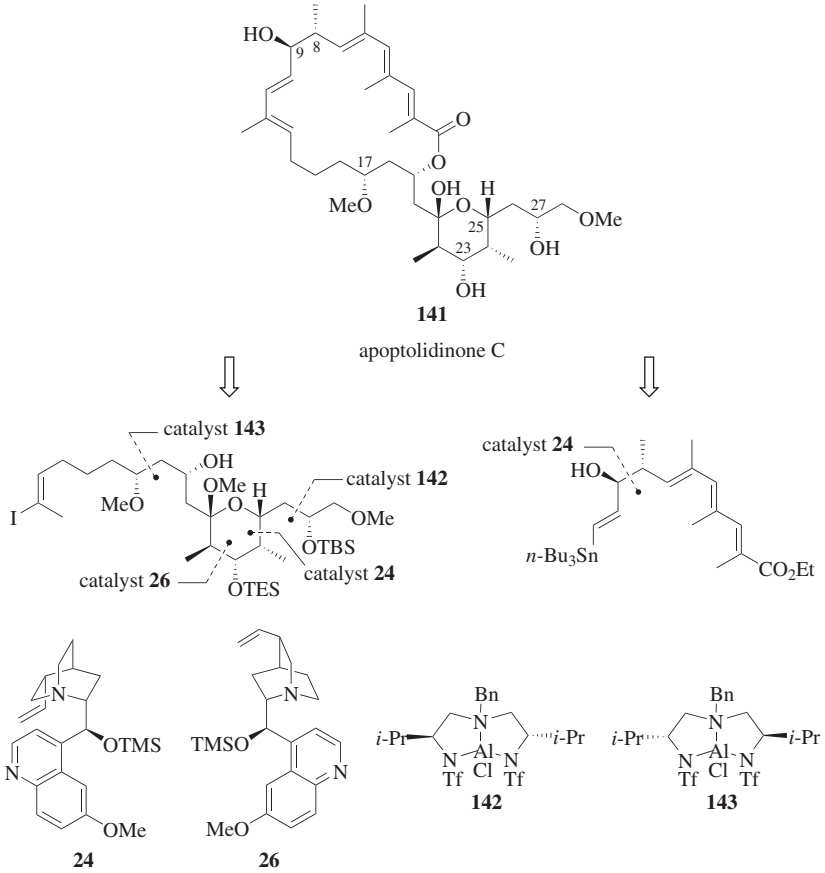
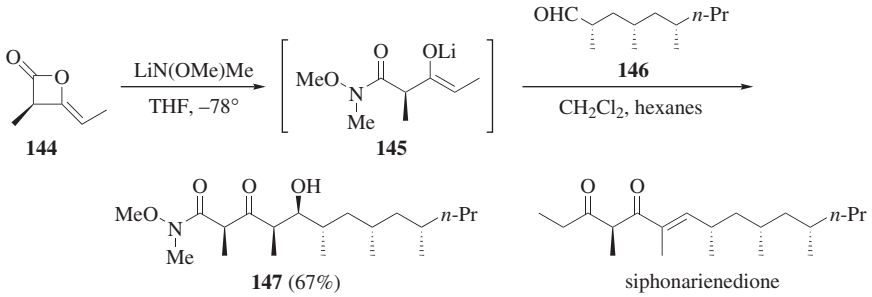


Figure 7. Lewis base and Lewis acid catalyzed [2 + 2] cycloadditions in the synthesis of apoptolidinone C.

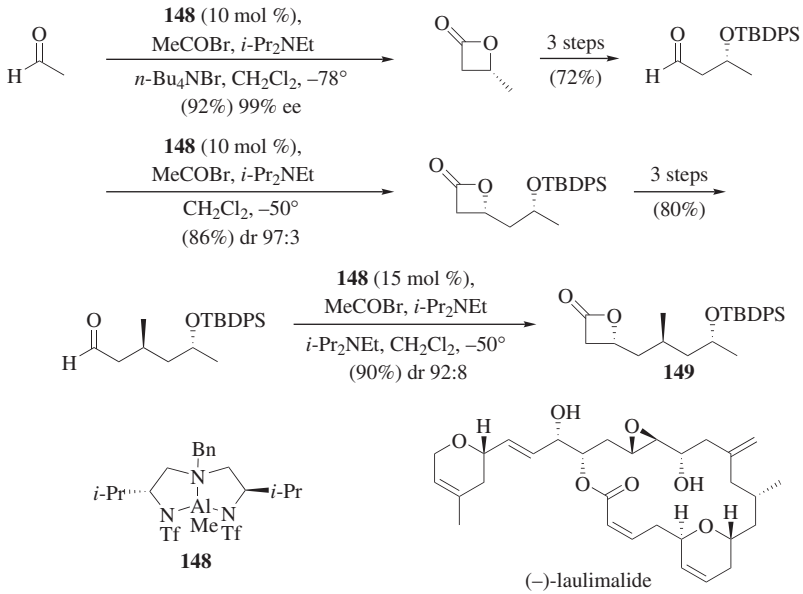
efficient route to enantioenriched β-keto amides and the utility of the derived enolates in asymmetric polyketide construction (Scheme 55).[152] Thus, ring opening of the enantioenriched methylketene dimer **144** with the lithium salt of *N*,*O*-dimethylhydroxylamine affords the corresponding β-keto amide enolate **145** that participates in a highly diastereoselective aldol addition with enantioenriched aldehyde **146** to afford the β-keto amide **147** (67%). Ensuing dehydration and amide-to-ethyl ketone conversion completes the siphonarienedione, total synthesis, thereby accessing, for the first time, a natural product possessing a rare configurationally stable stereogenic carbon at C2 of a 1,3-diketone.

Al(III)-Catalyzed Acyl Halide–Aldehyde Cyclocondensations. The utility of the Al(III)-catalyzed acyl halide–aldehyde cyclocondensations in complex molecule syntheses is evident in an asymmetric total synthesis of the naturally



Scheme 55

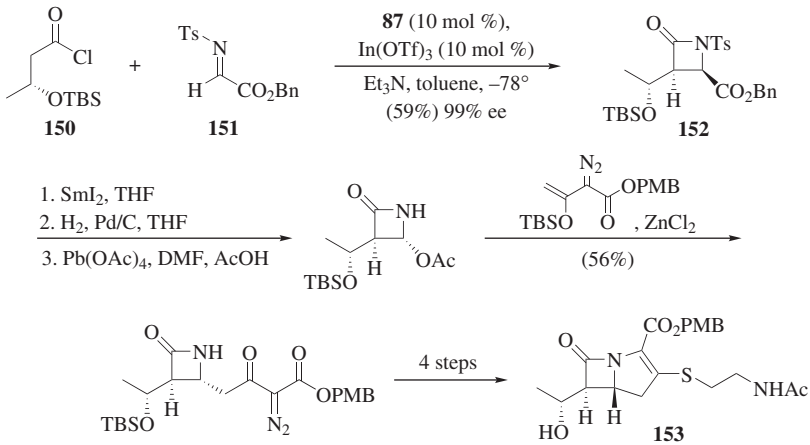
occurring anticancer agent (−)-laulimalide (Scheme 56).[153] Iterative application of the catalyzed ketene–aldehyde cycloadditions using the Al(III)–triamine catalyst **148** provides access to a series of 1,3-stereochemical relationships present in the C5–C14 synthon **149** integral to the total synthesis. Interestingly, the complementary modes available for nucleophilic β-lactone ring opening, either carbonyl addition–elimination or C4 nucleophilic substitution, are exploited to establish both oxygen- and methyl-bearing stereocenters present in the laulimalide fragment.[154]



Scheme 56

Alkaloid-Catalyzed [2 + 2] Ketene–Imine Cycloadditions. Despite the seemingly logical use of ketene–imine cycloadditions and the derived

2-azetidinone cycloadducts to the synthesis of β-lactam-containing chemotherapeutic agents, applications of catalytic asymmetric ketene–imine cycloadditions for this purpose are relatively rare. The asymmetric synthesis of carbapenem derivatives alludes to the potential of catalytic asymmetric ketene–imine cycloadditions for the synthesis of complex target molecules (Scheme 57).[155] Dehydrohalogenation of acid chloride **150** and subsequent reaction of the resulting ketene with α-imino ester **151** using the Lewis base–Lewis acid co-catalyst system composed of *O*-benzoylquinidine (**107**) (10 mol %) and $In(OTf)_3$ (10 mol %) affords the *cis*-disubstituted β-lactam **152** as a single stereoisomer (59%). β-Lactam **152** is subsequently converted into the *N*-acetyl thienamycin 4-methoxybenzyl ester (**153**) wherein conversion of **152** to the corresponding *N*,*O*-acetal with concomitant inversion at C4[156] and ensuing annulation to the [3.2.0] ring system constitute key steps enroute to the target.



Scheme 57

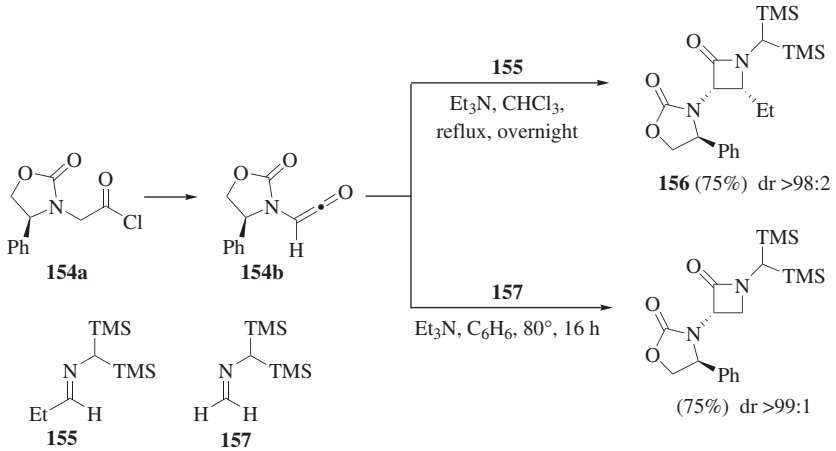
COMPARISON WITH OTHER METHODS

The fundamental importance of β-lactams in biomedicine has inspired an extensive body of research devoted to methods for accessing these materials by chemical synthesis, of which Staudinger-type cycloadditions are but one example. Similarly, the β-lactone and 2-pyranone products of [2 + 2] and [4 + 2] ketene cycloadditions, respectively, offer sufficient utility in synthetic enterprises that a variety of strategies for preparing these materials complementary to ketene cycloadditions have evolved. As the catalytic asymmetric reaction technologies highlighted herein are largely intended to access products absent preexisting chirality, this section is confined to methods designed to access enantioenriched reaction products wherein the stereocontrol element is transparent or is readily removed from the reaction products. Accordingly, diastereoselective reactions involving chiral auxiliaries are discussed in this section while diastereoselective reactions exploiting resident chirality that either is not intended to be or is

otherwise difficult to excise from the reaction product are described only when they have special relevance to the catalytic asymmetric ketene cycloadditions.

Diastereoselective [2 + 2] Cycloadditions

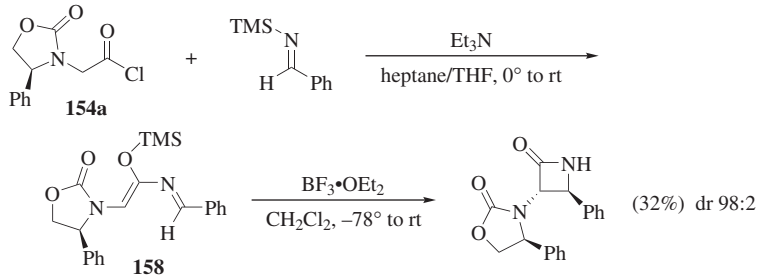
Ketene–Imine Cycloadditions. The broad utility of β-lactams as chemotherapeutic agents and the unmatched efficiency offered by Staudinger-type reactions for the synthesis of these important heterocycles has inspired extensive efforts to develop generally useful, asymmetric Staudinger processes.[157,158] Despite the advantages offered by asymmetric, catalytic reaction variants, transformations relying on chiral auxiliaries to control stereoselection can provide complementary strategies to access enantioenriched β-lactams.[10] As a result, early development of asymmetric Staudinger reactions was guided by the design and development of chiral auxiliaries that would influence the stereochemically defining electrocyclic ring closure event. These design efforts were facilitated by opportunities to incorporate the requisite chiral controllers in either the imine or ketene reaction components. For example, the oxazolidinone-substituted acid chloride **154a** is converted into the corresponding ketene **154b**[159–162] that reacts with *N*-alkyl aldimine **155** to afford the 3-amino-2-azetidinone **156** with extermely high asymmetric induction (Scheme 58).[163–165] Aldimine substrates for these reactions employ a bis(trimethylsilyl)methyl group on nitrogen to stabilize the imine tautomer, allowing reactions to be performed on enolizable imines.[166,167] The stability conveyed to the derived imines by *N*-bis(trimethylsilyl)methyl substitution is evident in the highly diastereoselective cycloadditions of the formaldehyde-derived imine **157** that, in the absence of this substituent, is highly unstable and prone to trimerization.[165]



Scheme 58

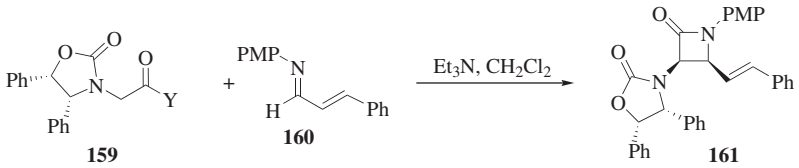
In an investigation that lends insight into the electrocyclic ring closure mechanism believed operative in these Staudinger reactions, **154a** reacts with (*E*)-1-phenyl-*N*-(trimethylsilyl)methanimine to afford isolable *N*-alkenyl imine **158**

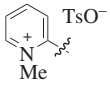
(Scheme 59).[168,169] Reacting the neutral ketene acetal **158** with $BF_3{\bullet}OEt_2$ initiates electrocyclic cyclization to afford the *trans*-disubstituted 2-azetidinone with good diastereoselectivity for aryl imine substrates but little selectivity for the pivaldehyde-derived imine.



Scheme 59

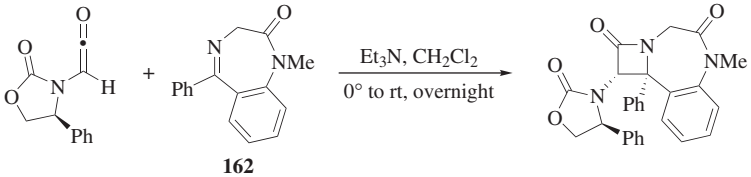
The closely related oxazolidinone-substituted carboxylic acid derivative **159** serves as a precursor to enantioenriched ketenes that engage *N*-aryl imines in highly diastereoselective Staudinger reactions (Scheme 60).[170,171] The observation that the α,β-unsaturated imine **160** delivers the β-lactam **161** exclusively is suggestive of these reactions' intrinsic kinetic preference for four-membered-ring formation, even when opportunities for competing six-membered-ring formation exist. The same oxazolidinone-substituted ketene also affords excellent diastereoselection in cycloadditions involving highly functionalized imine substrates such as the heterocyclic imine **162** (Eq. 36).[172]



Y	Temp (°)	Yield (%)	dr
Cl [a]	–78 to 0	60	98:2
	rt	97	94:6

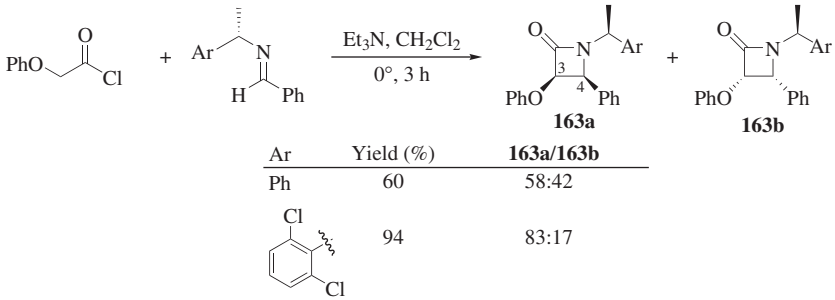
[a] This reaction is *ent*-**159** + *ent*-**160** yields *ent*-**161**.

Scheme 60



(Eq. 36)

Chiral auxiliaries are readily incorporated into the imine substrate of Staudinger reactions by condensing the appropriate enantioenriched amine with the requisite carbonyl compound. Enantioenriched imines derived from the ubiquitous α-methylbenzylamine afford negligible diastereoselection in Staudinger processes (Scheme 61); however, appropriate derivatization of the aryl residue in the chiral auxiliary leads to substantial improvements in the diastereoselection obtained for **163**.[173]

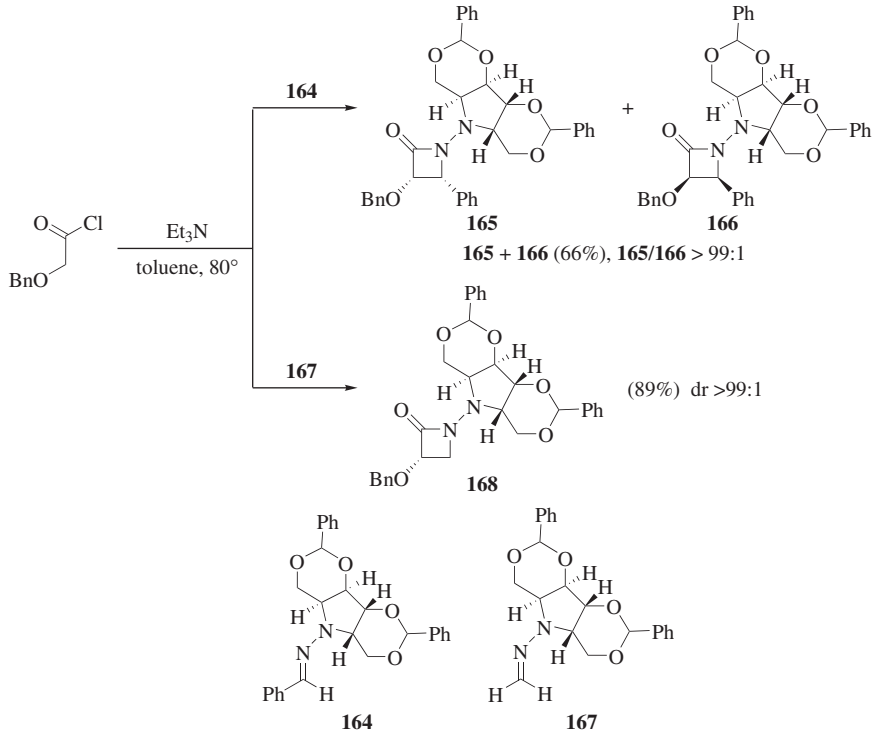


Ar	Yield (%)	163a/163b
Ph	60	58:42
	94	83:17

Scheme 61

Enantioenriched hydrazones serve as especially effective substitutes for simple imines in auxiliary-controlled asymmetric Staudinger reactions.[174] A variety of *N*-aminopyrrolidine-derived hydrazones engage achiral ketenes in highly diastereoselective Staudinger reactions.[175] Thus, the mannitol-derived hydrazone **164** mediates highly diastereoselective Staudinger cycloadditions with benzyloxyketene, generated in situ from the corresponding acid chloride, to afford the *cis*-disubstituted β-lactam **165** with diastereomer ratios exceeding 99:1 (**165/166**) (Scheme 62).[174,175] Unlike the oxazolidinone auxiliaries integrated into ketene substrates, straightforward procedures exist for cleaving chiral auxiliaries from the hydrazone-containing cycloadducts, typically under oxidative conditions, albeit with loss of the auxiliary.[176] Hydrazone substrate **167** affords access to enantioenriched β-lactam **168** unsubstituted at C4, an example of a family of heterocycles that is not easily accessed using existing catalytic asymmetric method.[177] Nonetheless, despite the success of these diastereoselective reaction variants employing chiral auxiliaries, reaction efficiency can be compromised relative to their asymmetric catalytic counterparts by the requirement to prepare, install, and remove the chiral controller.

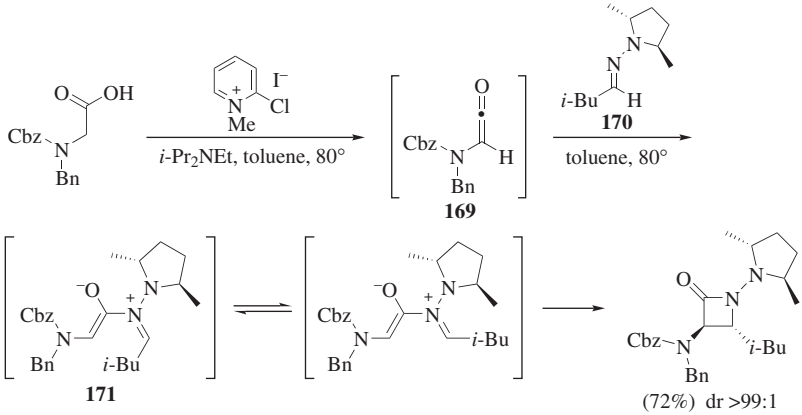
The stereochemical outcome of these hydrazone-controlled Staudinger cycloadditions exhibits a strong dependence on the identity of the ketene substituent. In contrast to the *cis*-disubstituted β-lactams emerging from the cycloadditions of enantioenriched hydrazone-derived imines, the carbamate-substituted ketene **169** reacts with chiral imine **170** to afford the *trans*-β-lactam to the near exclusion of the *cis* diastereomer (Scheme 63).[178] Steric impediment incurred by the large carbamate moiety during putative conrotatory electrocyclic ring closure of the kinetically formed zwitterion **171** is suggested as the origin of the unanticipated *trans* diastereoselection. As a result, ring



Scheme 62

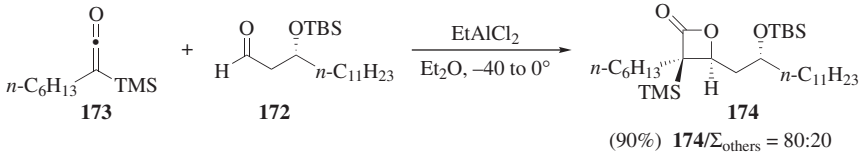
closure is slow relative to the (*E*) to (*Z*) iminium ion isomerization preceding conrotatory ring closure that avoids severe developing non-bonded interactions and affords the *trans*-β-lactam. Hydrazone-derived imines, therefore, provide another strategy for accessing stereochemically complementary β-lactams from a common reaction manifold. However, effectively employing this reaction strategy to access both *cis*- and *trans*-disubstituted enantioenriched β-lactams requires that these synthetic endeavors be confined to those requiring benzyloxy- or carbamate-substituted ketenes.

Ketene–Aldehyde Cycloadditions. While information on substrate-based stereocontrol in ketene–carbonyl cycloadditions is scarce compared to that accumulated for the ketene–imine cycloadditions, diastereoselectivity in ketene–aldehyde cycloadditions is quite responsive to preexisting stereocenters located at both the α and β positions of the aldehyde electrophile. Diastereoselection in ketene cycloadditions involving chiral α- and β-substituted aldehydes is generally consistent with the chelate–Cram, Felkin–Ahn, and Reetz–Evans models used to interpret traditional nucleophilic additions to analogous electrophiles.[41–43,179–181] Thus, the β-silyloxy aldehyde **172** participates in Al(III)-mediated cycloaddition with the disubstituted ketene **173**

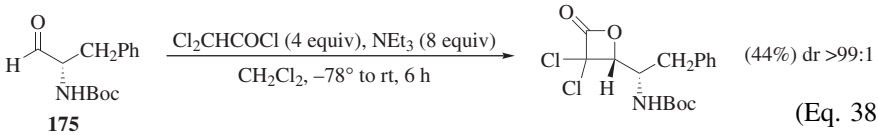


Scheme 63

to afford β-lactone **174** as the major diastereomer (Eq. 37).[182,183] Chelate–Cram selectivity is operative in the [2 + 2] cycloaddition of α-amino aldehyde **175** to afford the 2,3-*syn*-β-lactone that is consistent with cycloaddition proceeding via the aldehyde possessing an intramolecular H-bond to the proximal carbamate (Eq. 38).[18,184]



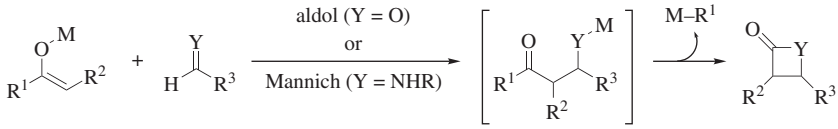
(Eq. 37)



(Eq. 38)

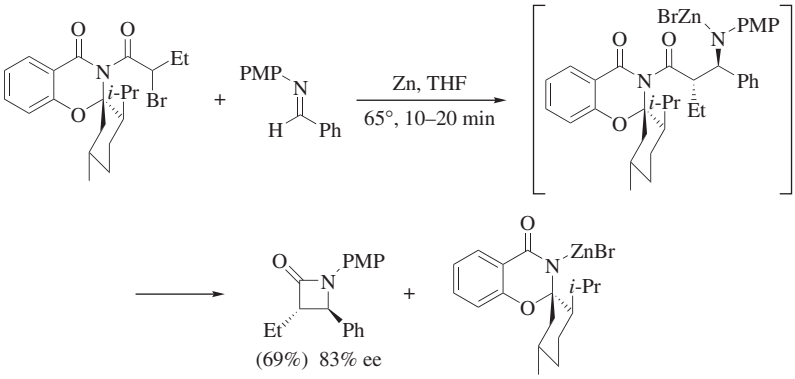
[2 + 2] Cycloadducts from Enolate Addition Reactions

Reaction Design. The structural homology that exist between traditional aldol addition and Mannich reaction adducts and the corresponding β-lactones and β-lactams, respectively, implicates these well-established C–C bond forming reactions as conduits to the corresponding four-membered heterocycles. Indeed, convenient methods for engaging the acyclic β-hydroxy carbonyl aldol or β-amino carbonyl Mannich adducts in intramolecular ester or amide bond formation, respectively, provide an attractive alternative to the corresponding ketene-based cycloadditions (Scheme 64).



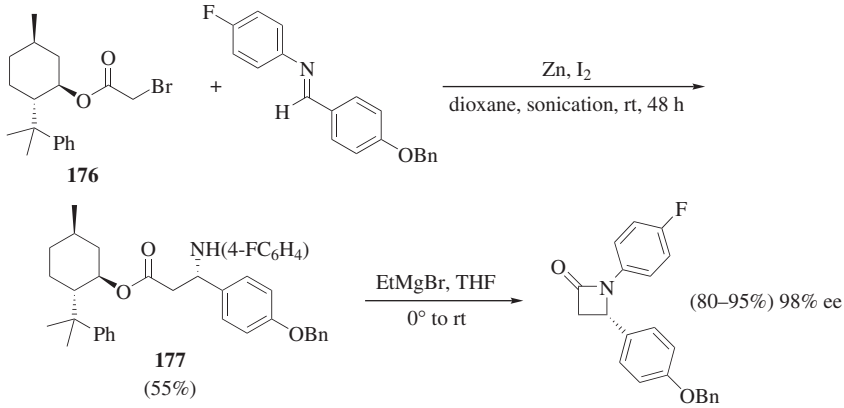
Scheme 64

Mannich-Based Approaches to β-Lactams. Enolate additions to *N*-aryl imine electrophiles can result in tandem reaction processes leading directly to enantioenriched β-lactams.[185] Zinc enolates generated under Reformatsky conditions[186] add to *N*-aryl imines to afford the corresponding zinc amides that, upon warming, cyclize to the corresponding β-lactam (Scheme 65).[187,188] In this example, the chiral auxiliary is cleaved from the β-lactam in the course of the cyclization. Similarly, the zinc enolate obtained from the 8-phenylmenthol-derived 2-bromoacetate **176** undergoes highly diastereoselective addition to an *N*-aryl aldimine to deliver the β-amino ester **177** that, upon treatment with base, cyclizes to the 4-substituted azetidinone in good yield and high enantioselectivity (98% ee) (Scheme 66).[189] As with the complementary Staudinger reactions, chiral controllers can also be incorporated within the imine electrophile. Under Reformatsky conditions, the chiral oxazolidine **179** acts as a latent imine and reacts with the zinc enolate derived from **178** to afford the 3,3-difluoro-2-azetidinone with high diastereoselectivity (Eq. 39).[190,191]



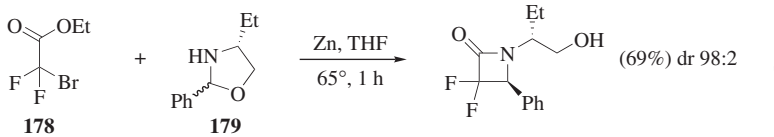
Scheme 65

Alkali and transition-metal enolates participate in similar tandem Mannich-cyclization processes thereby allowing traditional strategies for effecting asymmetric ester or amide enolate–imine additions to be correlated to stereoselective β-lactam syntheses. Lithium enolates of ephedrine-derived amides exhibit excellent diastereoselection in additions to *N*-4-methoxyphenyl aldimines, delivering the Mannich adducts such as **180** with near perfect relative stereocontrol (Scheme 67).[192–194] Subsequent amide hydrolysis and esterification of the resulting carboxylic acid gives the β-amino ester **181**. Reaction of ester **181** with

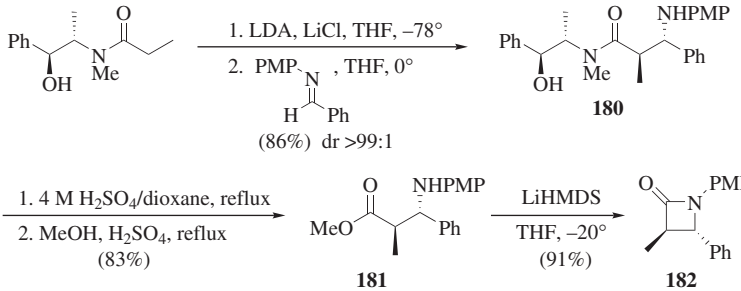


Scheme 66

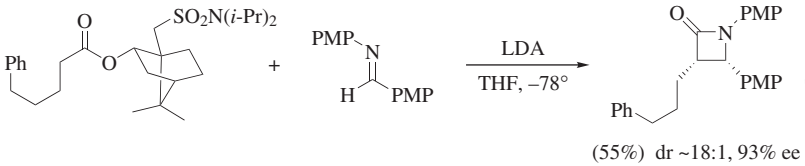
LiHMDS effects amine deprotonation and lactamization to afford **182** as a single diastereomer. In one example, an ester enolate incorporating an isoborneol sulfonamide chiral auxiliary also delivers high diastereoselectivity in a tandem Mannich addition–lactamization process to afford the *cis*-β-lactam in moderate yield but high enantioselectivity (Eq. 40).[195]



(Eq. 39)

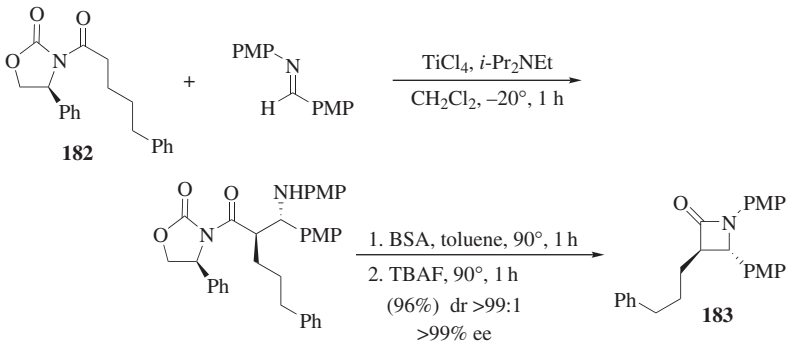


Scheme 67

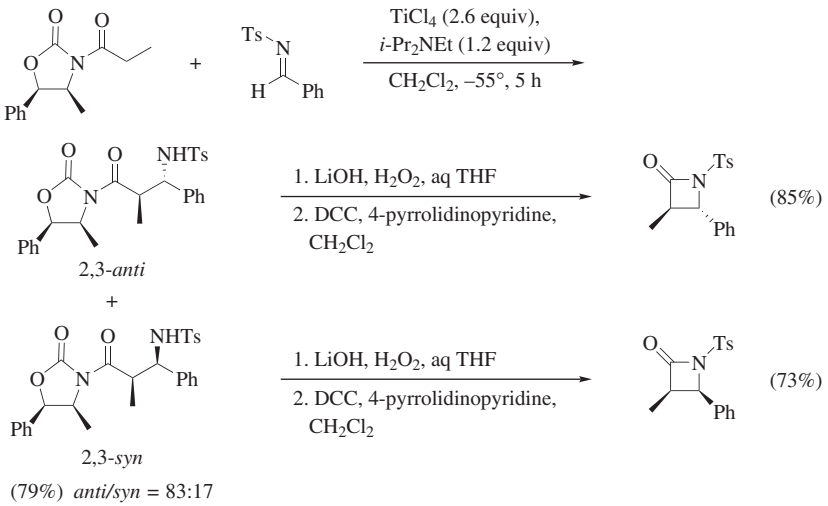


(Eq. 40)

In contrast to the reliability and efficiency that characterizes enolate additions involving ubiquitous *N*-acyl oxazolidinones, Mannich-type processes provide the rare example of enolate-based bond constructions for which oxazolidinone auxiliaries do not provide a satisfactory solution.[196,197] The titanium enolate obtained from *N*-acyl oxazolidinone **182** participates in highly diastereoselective addition to an aryl Schiff base to afford, after cyclization of the intervening β-amino imide, the *trans*-β-lactam **183** with nearly perfect relative and absolute stereocontrol (Scheme 68).[198] However, closely related *N*-acyloxazolidinone-derived enolates add to *N*-tosyl imines with only modest diastereoselection (Scheme 69).[199] In this instance, the Mannich adduct diastereomers can be separated, cleaved with $LiOH/H_2O$, and the resulting carboxylic acid is cyclized with dicyclohexylcarbodiimide (DCC) and 4-pyrroldinopyridine to afford the *cis*- and *trans*-β-lactams.

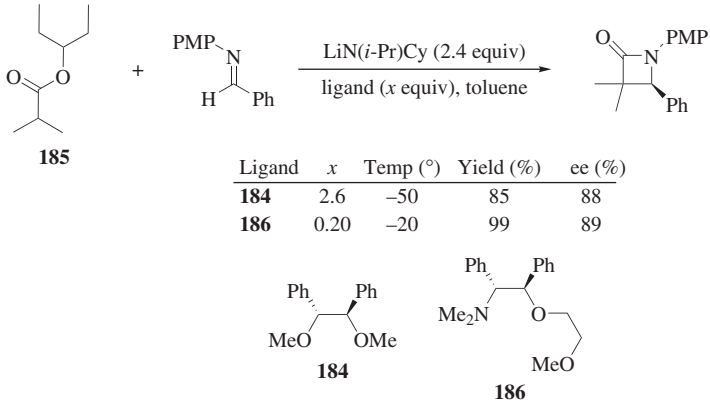


Scheme 68



Scheme 69

Ligand-modified metalloenolates provide another strategy for stereocontrol in enolate-electrophile additions without requiring that the chiral auxiliary be covalently linked to either of the reaction substrates. Lithium ester enolates modified with stoichiometric quantities of enantioenriched, chelating ligands afford useful enantioselectivities in additions to *N*-(4-methoxyphenyl)aldimines (Scheme 70).[200,201] In these reactions, lithium amide and ligand structures are critical to defining reaction efficiency; β-lactam enantioselectivity is optimized for 1,2-dimethoxy-1,2-diphenylethane (**184**, 2.6 equiv) using lithium *N*-isopropyl cyclohexylamide (2.4 equiv) as the base.[200] The observation that the ligands accelerate the enolate–imine addition rate suggest that useful levels of induction can be achieved using substoichiometric quantities of the ligand, based on the premise that the achiral, non-chelated enolate would be kinetically less competent relative to the enantioenriched-ligand-modified nucleophile. Indeed, the lithium enolate derived from ester **185** reacts with the imine in the presence of amino diether **186** (20 mol %) to provide the enantioenriched β-lactam in nearly quantitative yield (89% ee).[201] As with the reaction using stoichiometric quantities of the ligand, high enantioselectivities are maintained for aryl imines but erode considerably for aliphatic imine electrophiles. Moreover, useful levels of induction are limited to achiral α,α-disubstituted ester enolate precursors that afford β-lactam products incorporating non-stereogenic quaternary C3 carbons.

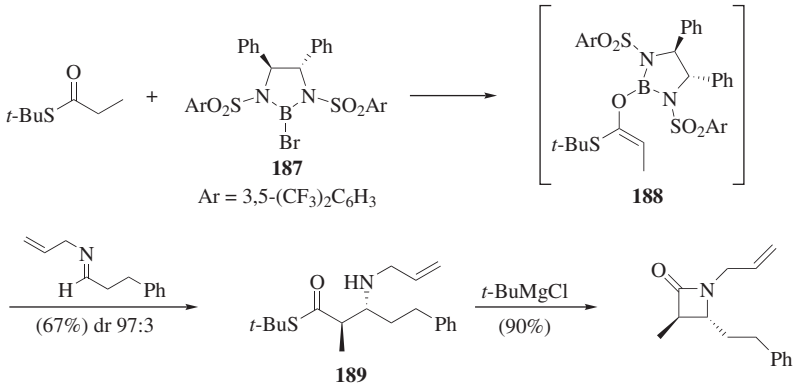


Ligand	*x*	Temp (°)	Yield (%)	ee (%)
184	2.6	–50	85	88
186	0.20	–20	99	89

Scheme 70

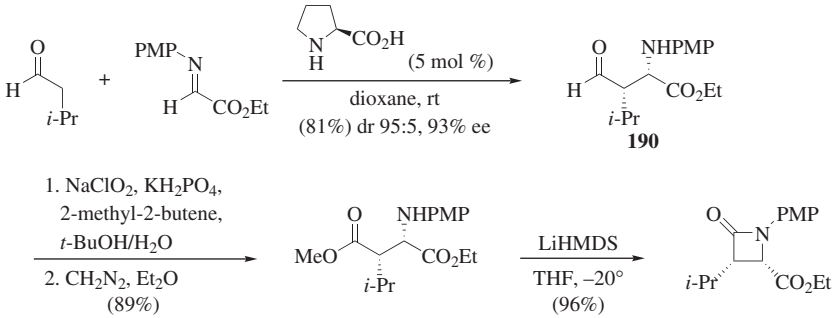
Boron-modified enolates and enolate surrogates are especially useful in the design and development of asymmetric transformations where asymmetric induction is derived from the ligands associated with boron. The chiral bromoborane reagent **187** is used to generate enantioenriched thioester enolate **188** that adds to an *N*-alkyl aldimine to afford the *anti*-Mannich adduct **189** with high enantioselectivity (Scheme 71).[201] Subsequent amine deprotonation promotes addition-elimination to the adjacent thioester to afford the β-lactam. Relative to catalytic asymmetric approaches to related β-lactams, the efficiency of these auxiliary-mediated strategies can suffer from the multiple operations required to convert the

initial Mannich adduct into the β-lactam. However, the *trans*-β-lactams afforded by the latter two approaches are not easily accessed by existing catalytic, asymmetric reaction designs.



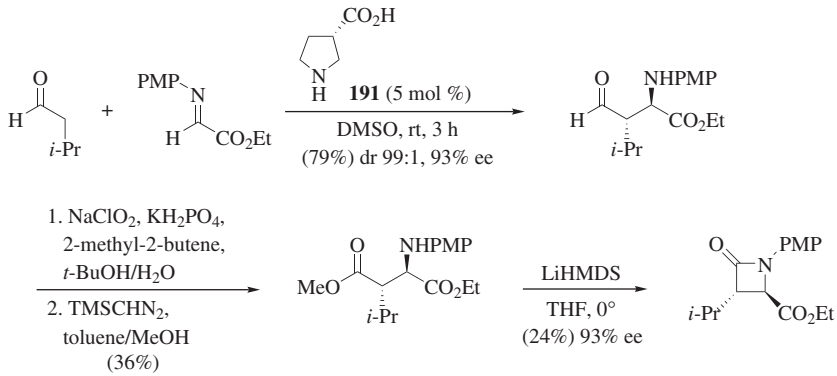
Scheme 71

A more direct comparison of β-lactam syntheses based on catalytic, asymmetric Staudinger processes relative to approaches based on enolate–imine addition-based is derived from asymmetric, direct Mannich reactions.[203,204] Thus, (*S*)-proline-catalyzed addition of aldehydes to α-imino esters affords the enantioenriched aspartic acid derivative **190** with high enantioselectivity (Scheme 72).[205] Following aldehyde oxidation to the corresponding acid and ester, amine deprotonation induces cyclization to afford the *cis*-disubstituted β-lactam with enantiomeric purity reflective of the β-amino ester precursor.The analogous *anti*-selective Mannich reaction catalyzed by **191** affords access, by a similar reaction sequence, to the complementary *trans*-disubstituted β-lactam (Scheme 73).[206] These reactions share with the alkaloid-catalyzed Staudinger reactions similarly high enantioselectivities and the requirement for highly electrophilic,



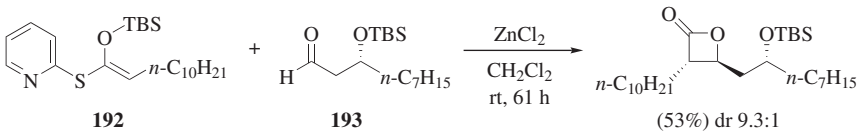
Scheme 72

non-enolizable α-imino ester substrates. The 3-pyrrolidinecarboxylic acid-catalyzed reactions are an attractive complement to existing catalytic, asymmetric Staudinger processes as they afford the *trans*-disubstituted β-lactams, albeit in a multistep sequence from the initial Mannich adduct.

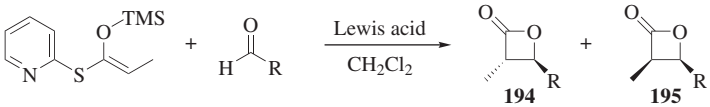


Scheme 73

Aldol-Based Approaches to β-Lactones. Tandem Mukaiyama aldol-lactonization reactions best exemplify the relationship existing between aldol-based bond constructions and the related β-lactones. The aldol lactonization reaction design allows β-lactones to be accessed directly from the aldol addition event by incorporating latent, activated esters into the enolate precursor. Thus, 2-pyridyl thioester derived enol silane **192** participates in Lewis acid mediated Mukaiyama aldol additions with the chiral β-substituted aldehyde **193** to directly generate the enantioenriched β-lactone exhibiting high 1,3-*anti*-diastereoselectivity as well as high *trans*-diastereoselection across the β-lactone (Eq. 41).[207] Reactions employing achiral aldehyde substrates are characterized by Lewis acid dependent diastereoselection, with $ZnCl_2$ delivering the *trans*-β-lactone products **194**, whereas $SnCl_4$ provides the *cis*-disubstituted β-lactone **195** as the major diastereomer (Scheme 74).[207,208] Accordingly, these reactions are distinguished from ketene-based cycloadditions by the ability to readily access either diastereomer from a single reaction manifold, a feature that is not a common characteristic among catalyzed ketene cycloadditions. Although no examples of catalytic, asymmetric tandem processes have been reported, the wealth of effective catalysts for asymmetric Mukaiyama-type aldol reactions offer potential strategies for developing enantioselective reaction variants.[113,209]



(Eq. 41)

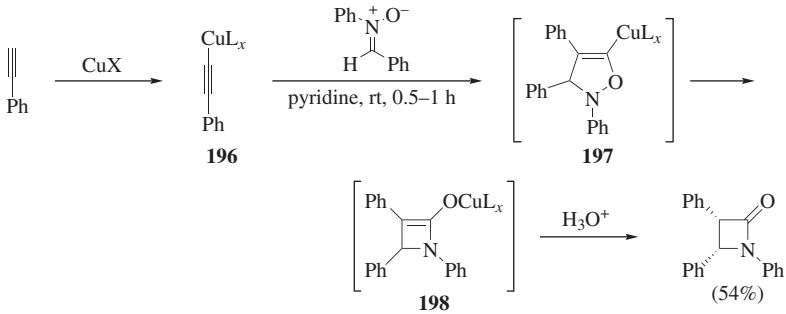


R	Lewis Acid	Temp (°)	**194** + **195** Yield (%)	**194/195**
$PhCH_2CH_2$	$ZnCl_2$	—	57	37:1
$PhCH_2CH_2$	$SnCl_4$	–78	62	<5:95
c-C_6H_{11}	$ZnCl_2$	—	16	>95:5
c-C_6H_{11}	$SnCl_4$	–78	9	1:2.3

Scheme 74

β-Lactams from Nitrone–Alkyne Cycloadditions

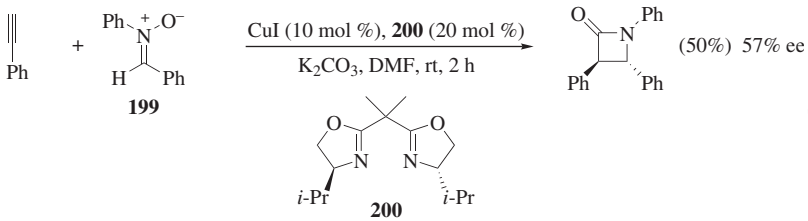
The thermal dipolar cycloaddition of nitrones with alkynes is among the most expedient syntheses of isoxazoline heterocycles. Activating the alkyne dipolarophile as the corresponding Cu(I) acetylide **196** accesses a new cycloaddition manifold leading to 2-azetidinones rather than the isoxazolines obtained using neutral alkynes (Scheme 75).[210] In fact, the initial cycloaddition pathway for each of these processes proceeds through the same isoxazoline structure **197**.[211] However, the organocopper intermediate **197** emerging form the copper acetylide cycloaddition undergoes ring contraction to generate the β-lactam Cu(I) enolate **198** that, upon work-up, affords the corresponding 2-azetidinone. Subsequent investigations revealed that the requisite copper acetylides can be generated in situ using substoichiometric amounts of a Cu(I) salt and that the resulting product distribution is sensitive to the structure and electronic nature of the ligands on the copper ion.[212] These investigations implicate the Cu(I) addend and the ligands associated with the metal center as vehicles for controlling the stereochemical outcome of what is now known as the Kinugasa reaction.[213,214]



Scheme 75

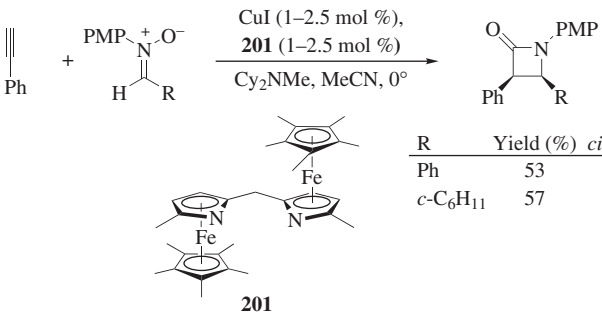
Bis(oxazoline) ligands are ubiquitous in catalyzed organic transformations using both Cu(I)- and Cu(II)-based Lewis acid catalysts.[215–217] It is not surprising, therefore, that initial attempts to realize an asymmetric Kinugasa reaction employ enantioenriched bis(oxazolines) as the modifying ligands for the copper acetylide intermediate.[213,218] Thus, nitrone **199** and phenylacetylene react

with CuI (10 mol %) and bis(oxazoline) **200** (20 mol %), using potassium carbonate as the base to generate the Cu(I)-acetylide, to afford the *trans*-β-lactam (50%, 57% ee) (Eq. 42).[219] Accompanying investigations reveal that the *cis*-β-lactam emerging from the initial cycloaddition is equilibrated to the more stable *trans*-diastereomer by heating the product mixture with potassium carbonate. Subsequent investigations would confirm that the *cis*-β-lactam is the kinetic product of these copper acetylide–nitrone cycloadditions.



(Eq. 42)

Substantial improvements in stereoselectivity of the Cu(I)-catalyzed Kinugasa reactions are achieved through the design of chelating diamine ligands creating a more effective chiral environment about the copper ion. The bis(azaferrocene) ligand **201** provides useful levels of enantioselection with concomitant improvements in the efficiency of the derived copper catalyst.[220] Thus, the low loadings of the complex from CuI and **201** (1–2.5 mol % each) catalyze the Kinugasa cycloaddition of *N*-aryl nitrones and terminal alkynes to afford the corresponding β-lactams in generally high enantioselectivities (Scheme 76). Tertiary amines are suitable for the in situ generation of the Cu(I) acetylide intermediate and provide the ancillary benefit of minimizing the *cis* to *trans* isomerization witnessed in similar reactions employing carbonate bases. As a result, *cis* diastereoselection in these reactions is uniformly high with the exception of one aliphatic, unbranched alkyne.[220]

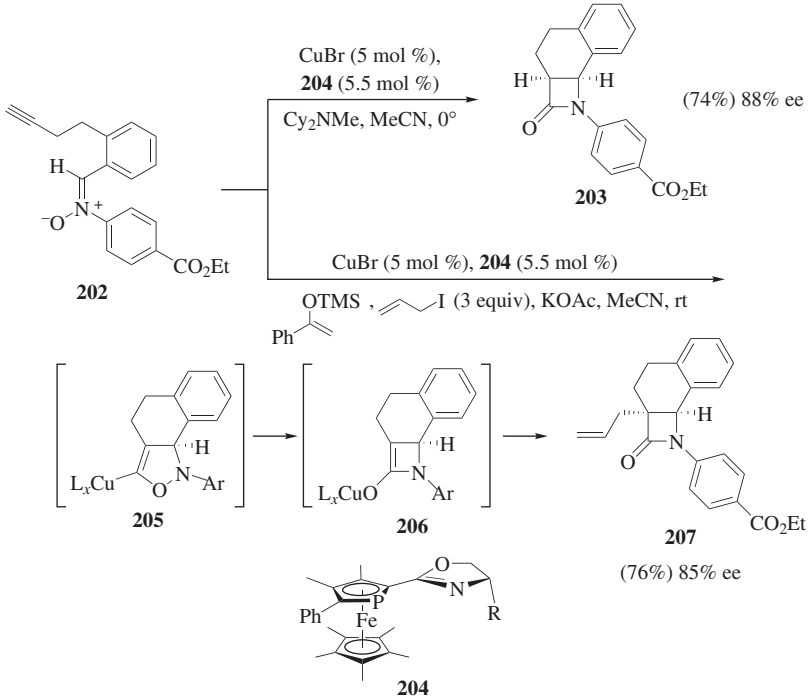


R	Yield (%)	*cis*/*trans*	ee (%) *cis*
Ph	53	95:5	85
c-C_6H_{11}	57	93:7	89

Scheme 76

Despite the special importance of fused, bicyclic β-lactams as antibiotic agents, developments in asymmetric, intermolecular processes for accessing β-lactams

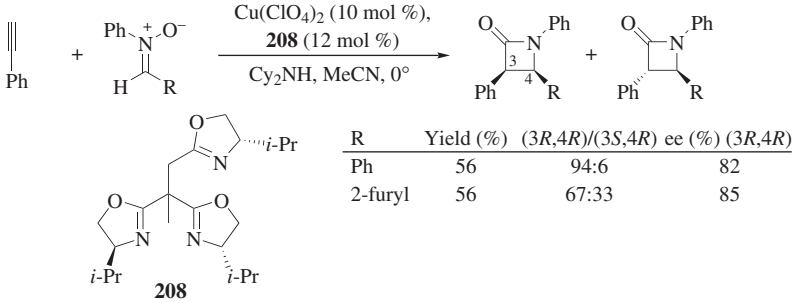
have not translated to intramolecular reactions that deliver polycyclic ring systems. Since *N*-aryl nitrones are readily prepared in the presence of terminal alkynes, the Kinugasa reaction provides an attractive platform of developing intramolecular processes accessing polycyclic, enantioenriched β-lactams. Planar-chiral heteroferrocene ligands again effect catalytic asymmetric Kinugasa reactions. Applying the reaction conditions optimized for the Cu(I)-bis(azaferrocene)-catalyzed reactions to alkyne-nitrone **202** affords bicyclic β-lactam **203**, albeit with dramatically decreased efficiency relative to the corresponding intermolecular reactions (Scheme 77).[221] However, substituting the bidentate phosphaferrocene ligand **204** for bis(azaferrocene) **201** provides a generally useful catalyst for intramolecular nitrone–alkyne cycloadditions leading to tricyclic C–aryl β-lactams (e.g. **203**). A mechanistic model for these reactions involving initial cycloaddition to form metallo-isoxazoline **205** and ensuing rearrangement to β-lactam enolate **206** suggests a strategy for realizing asymmetric quaternary carbon construction in concert with the Kinugasa cycloaddition. Provided enolate **206** resides on the reaction pathway, extensive precedent from cuprate–enone additions suggests that this enolate can be trapped with an appropriate electrophile. Indeed, including allyl iodide in the Cu(I)•**204**-catalyzed annulation of **202**, in conjunction with KOAc as the base for copper acetylide formation and an enol



Scheme 77

silane proton scavenger, provides the 3-allyl β-lactam **207** with enantioselectivity and chemical yield directly paralleling those obtained for the annulation alone.

Copper(I) acetylide reagents are most commonly generated in situ by combining a terminal alkyne and tertiary amine with a Cu(I) salt.[222] A catalytic asymmetric variant of the Kinugasa cycloaddition also provides insight into the reaction conditions and copper oxidation state required to generate copper-modified acetylide anions. For this variant of the nitrone–alkyne cycloadditions, the enantioenriched tris(oxazoline) ligand **208** activates divalent copper salts to form catalysts for asymmetric Kinugasa cycloadditions (Scheme 78).[223] The catalyst obtained from $Cu(ClO_4)_2$ (10 mol %) and **208** (12 mol %) effects the cycloaddition of various aryl nitrones and phenylacetylene to provide the *cis*-disubstituted β-lactams with good enantioselectivities. Cycloaddition efficiency is sensitive to the structure of the amine additive; reaction yield, diastereoselectivity, and enantioselectivity all vary with amine structure such that dicyclohexylamine provides optimum enantioselection and chemical yields in the Cu(II)-catalyzed cycloadditons. The Cu(II)-based catalyst system eliminates the requirement for inert atmosphere reaction conditions necessitated by Cu(I)-based catalysts to inhibit catalyst oxidation.



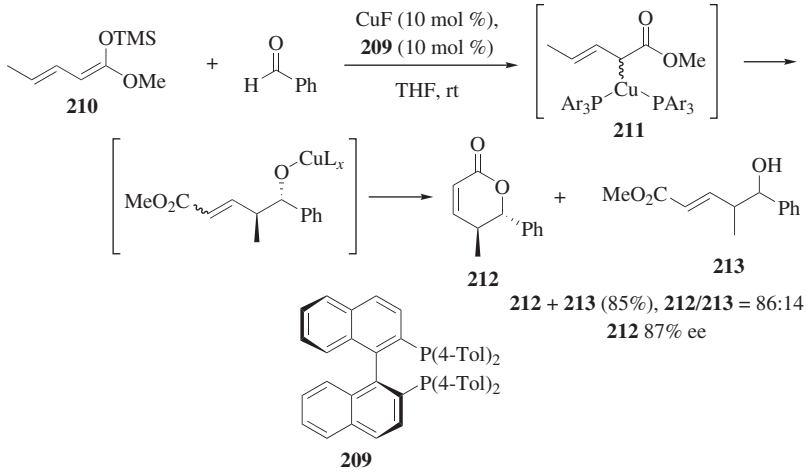
R	Yield (%)	(3*R*,4*R*)/(3*S*,4*R*)	ee (%) (3*R*,4*R*)
Ph	56	94:6	82
2-furyl	56	67:33	85

Scheme 78

Alternative Approaches to [4 + 2] Cycloadducts

Catalytic asymmetric [4 + 2] cycloadditions that employ ketene reaction components find close mechanistic and topological parallels in traditional hetero-Diels–Alder and inverse-electron-demand hetero-Diels–Alder cycloadditions. Electron-rich conjugated dienes behave similarly to alkenyl ketenes in hetero-Diels–Alder cycloadditions involving electrophilic carbonyl dienophiles and deliver nearly identical 5,6-dihydropyran-2-one cycloadducts.[224,225] The isomeric 3,4-dihydropyran-2-one products of enone–ketene cycloadditions emerge from analogous inverse-electron-demand hetero-Diels–Alder reactions, wherein electron-rich alkenes function as the requisite dienophiles.[226] Available modes of catalysis in these complementary cycloadditions are also closely aligned as both Lewis acid and Lewis base catalysis are operative in catalytic asymmetric hetero-Diels–Alder and inverse-electron-demand hetero-Diels–Alder reactions.

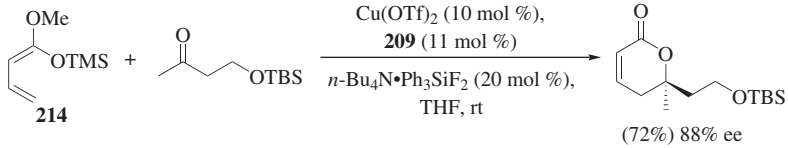
Hetero-Diels–Alder Reactions. Lewis acid catalyzed hetero-Diels–Alder reactions of electron-rich dienes and carbonyl dienophiles afford enantioenriched 5,6-dihydropyran-2-one cycloadducts closely analogous to those emerging from the alkenyl ketene–carbonyl cycloadditions. The catalyst complex derived from CuF and (*S*)-(−)-2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl (**209**) functions as both Lewis acid and Lewis base in mediating enantioselective formal [4 + 2] cycloadditions with carbonyl electrophiles.[227] Evidence from CuF-catalyzed Mukaiyama aldol additions suggests that 1-silyloxy diene **210** reacts with the catalyst complex to afford extended Cu(I) enolate **211** that is best represented as the Cu(I) allyl species (Scheme 79).[228–230] Addition of **211** to the carbonyl "dienophile" generates the enantioenriched vinylogous aldol adduct that cyclizes under the reaction conditions to afford δ-lactone **212**.[228] Formation of the enantioenriched [4 + 2] cycloadduct is accompanied by varying amounts of stereorandom, vinylogous aldol adduct **213** that does not undergo lactonization. These reactions are highly *anti*-selective for a variety of aromatic and aliphatic aldehydes, although nonaromatic aldehydes afford higher percentages of the acyclic aldol adducts.



Scheme 79

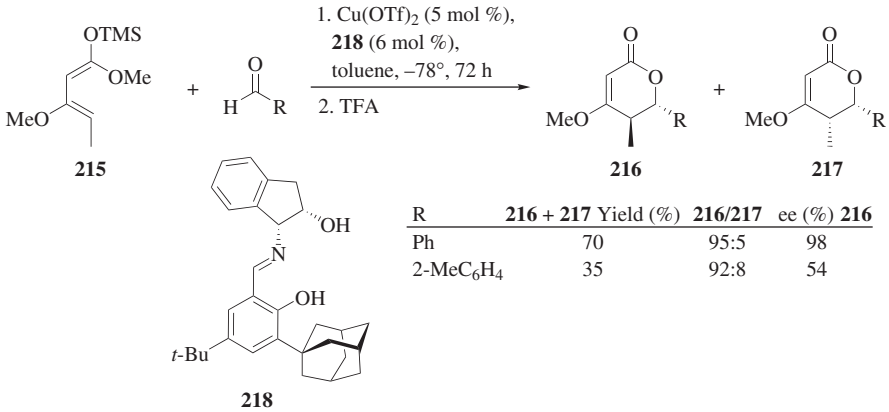
The Cu(II)–4-Tol-BINAP complex derived from CuF and BINAP **209** also catalyzes the cycloaddition of 1,1-dialkoxydienes lacking γ-substituents (e.g. **214**) with aryl and aliphatic ketone electrophiles, generating 6,6-disubstituted 2-pyranones with moderate to high enantioselectivities and good yields (Eq. 43).[231] This reaction mode differentiates these CuF-catalyzed cycloadditions from their Lewis base catalyzed alkenyl ketene counterparts as no reports of the latter using ketone electrophiles have appeared. Aside from this significant difference, these two hetero-Diels–Alder variants are very similar, accommodating similar substituents in the reaction partners, providing similar stereoselectivities and

requiring preparation of the requisite dienes, or diene precursors, from similar enone starting materials.



(Eq. 43)

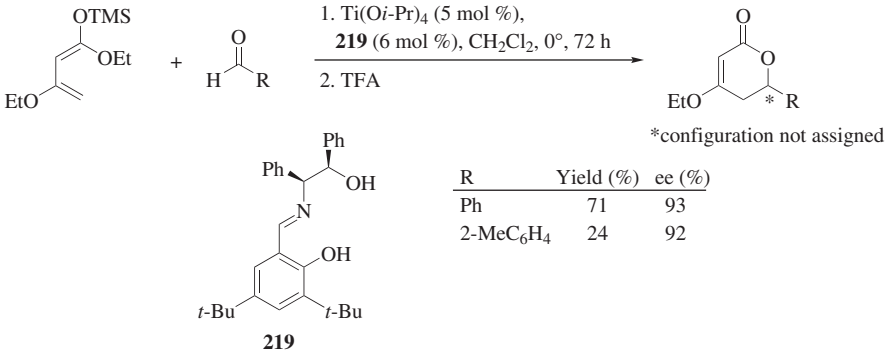
Enantioenriched 4-alkoxy-5,6-dihydropyran-2-ones **216** and **217** emerge from the cycloaddition of trialkoxy diene **215** with aryl aldehydes using the complex obtained from $Cu(OTf)_2$ and the Schiff base ligand **218** as catalyst (Scheme 80).[232] Reaction enantioselection is strongly dependent on substitution about the aryl aldehyde dienophile such that 4-substituted aldehydes generally afford high enantioselectivities whereas 2-substituted substrates afford much lower selectivities. Isolated yields of the enantioenriched pyranones are moderate for aryl aldehydes (40–70%) while aliphatic and α,β-unsaturated aldehydes are not effective substrates. The closely related Schiff base ligand **219** in conjunction with Ti(IV) catalyst precursors constitute useful catalysts for related hetero-Diels–Alder reactions involving dienes lacking C4-substituents (Scheme 81).[233,234] While no definitive mechanistic data is provided regarding the course of these reactions, the catalytic competence of high oxidation state copper and titanium complexes suggest that simple Lewis acid activation of the aldehyde dienophile is responsible for catalysis.



R	**216** + **217** Yield (%)	**216/217**	ee (%) **216**
Ph	70	95:5	98
2-MeC_6H_4	35	92:8	54

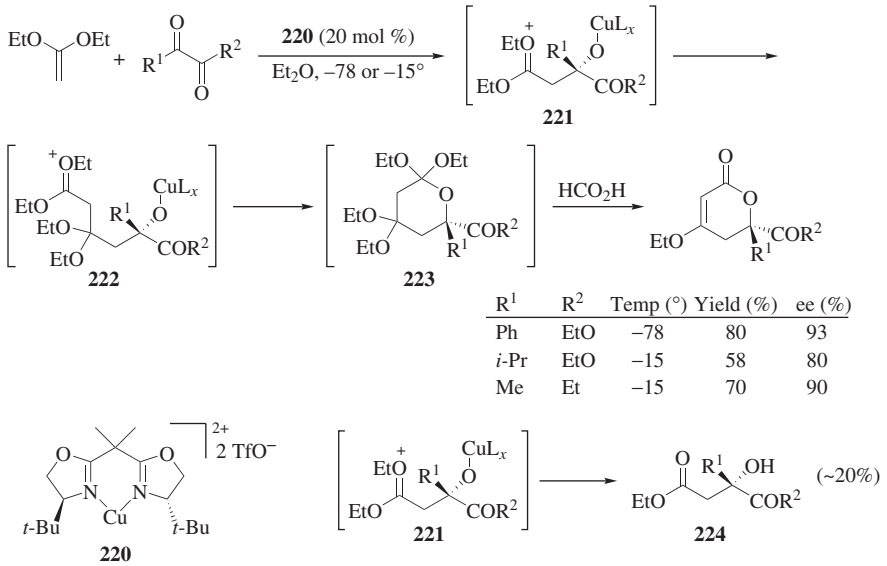
Scheme 80

Ligand-modified Cu(II) complexes also provide access to closely related 4-alkoxy 2-pyranones via a multicomponent condensation of ketene acetals and α-diketone electrophiles (Scheme 82).[235] Catalysts and reaction components for



R	Yield (%)	ee (%)
Ph	71	93
2-MeC$_6$H$_4$	24	92

Scheme 81



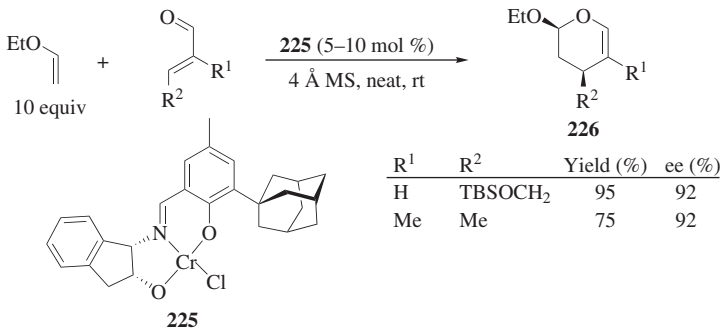
R^1	R^2	Temp (°)	Yield (%)	ee (%)
Ph	EtO	–78	80	93
i-Pr	EtO	–15	58	80
Me	Et	–15	70	90

Scheme 82

these formal [4 + 2] cycloadditions parallel closely those utilized in Cu(II)-catalyzed trimethylsilylketene-α-dicarbonyl [2 + 2] cycloadditions.[116] The composition of Cu(II)-bis(oxazoline) catalyst **220** and the derived chelate organization of the α-dicarbonyl substrate (see **68** in Eq. 16) are identical. However, replacing the trimethylsilylketene that propagates the [2 + 2] pathway with ketene diethylacetal enables an alternative formal [4 + 2] reaction pathway accessing enantioenriched 2-pyranone derivatives. These multicomponent cycloadditions proceed by nucleophilic attack of the electron-rich alkene on the Cu(II)-coordinated α-diketone, generating oxocarbenium ion intermediate **221**. The oxocarbenium

ion reacts further with the ketene acetal to produce a new oxocarbenium ion **222** that cyclizes to **223** with concomitant catalyst regeneration; direct collapse of the initial oxocarbenium ion **221** to give the mono-addition adduct **224** constitutes a minor reaction pathway (~20%). Consistent with the preceding Cu(II)-catalyzed [2 + 2] cycloadditions, 5 mol % of the Cu(II)-bis(oxazoline) catalyst engages a variety of pyruvates and α-diketones as substrates with unsymmetrical α-diketones being highly chemoselective for the sterically less hindered carbonyl residue to afford polyoxygenated pyrans **223** as the initial cycloadducts. Acid-mediated hydrolysis of **223** librates the enantioenriched δ-lactones.

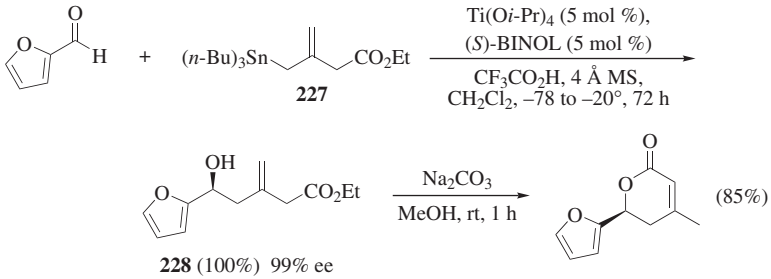
The homology existing between ketene-based [4 + 2] cycloadditions and their more traditional counterparts continues in inverse-electron-demand hetero-Diels–Alder reactions. Both Diels–Alder variants share the use of α,β-unsaturated carbonyl compounds as electron-deficient dienes while electron-rich alkenes take the place of ketene as the dienophile to deliver enantioenriched, substituted pyran cycloadducts. Enantioenriched Cr(III)-Schiff base complex **225** serves as the catalyst for highly enantioselective vinyl ether–enone cycloadditions providing unsaturated acetal cycloadducts **226** (Scheme 83).[236] The Cr(III)-based catalyst system accommodates a variety of enal dienes incorporating alkyl, aryl, and heteroatom-containing substituents at C4. Moreover, these reactions require no solvent beyond the ethyl vinyl ether that is used in ten-fold excess.



R^1	R^2	Yield (%)	ee (%)
H	$TBSOCH_2$	95	92
Me	Me	75	92

Scheme 83

Catalytic Asymmetric Allylation-Lactonization. Strategies for δ-lactone synthesis based on the lactonization of acyclic precursors enable catalytic, asymmetric carbonyl addition reactions as potential conduits to enantioenriched 2-pyranones. For example, a highly efficient synthesis of 5,6-dihydropyran-2-ones emerges from the Ti(IV)–BINOL-catalyzed addition of allylstannane **227** to aldehydes that affords the homoallylic alcohol **228** with extremely high enantioselection (Scheme 84).[237] The ensuing lactonization of δ-hydroxy ester **228** under basic condition proceeds with olefin isomerization to afford the 2-pyranones.



Scheme 84

EXPERIMENTAL CONDITIONS

Most ketenes are highly reactive species that must be prepared immediately prior to their use in a reaction or that they be generated in situ. Highly reactive ketenes, such as ketene itself or alkyl ketenes, are prepared as solutions in organic solvents and used immediately in subsequent reactions. Ketene solutions are generated by pyrolyzing acetone vapors and collecting the gaseous ketene by bubbling it into organic solvents (e.g., THF, toluene) at low temperatures.[63,64,84,238] Anhydride pyrolysis[85,149] or Zn-mediated dehalogenation of 2-bromopropionyl bromide[84,86] are used to generate gaseous methylketene that is, again, trapped as a solution in organic solvents at low temperature. For dimerization reactions where only the ketene substrate and catalyst are required, the catalyst can be present in the solvent trap, allowing the dimerization reaction to proceed as the ketene is collected.

Ketenes possessing substituents that attenuate their proclivity toward thermal dimerization can be prepared in advance and isolated. For example, alkyl aryl ketenes are prepared by amine-mediated dehydrohalogenation of acid chlorides and the resulting ketenes are isolated by distillation.[239] Trimethylsilylketene is sufficiently stable under ambient conditions that it is available for purchase from commercial suppliers.

Substrate generality and operational expediency are, typically, maximized for reactions that integrate in situ ketene generation into the reaction design. Amine-mediated dehydrohalogenation of acid chlorides is the most commonly used procedure for integrating ketene generation into the reaction cycle.[69,240] This technique allows ketenes to be accessed from commercially available or easily prepared acid chlorides and, for the most part, eliminates the requirement for utilizing isolable ketenes. Acid chloride precursors afford access to ketene, alkyl ketenes, heteroatom-substituted ketenes, and disubstituted ketenes. Although a variety of bases may be used for this purpose, tertiary amines are most commonly used due to their ready availability and comparatively low cost. The most effective bases are, generally, non-nucleophilic to minimize acyl ammonium ion formation that can inhibit ketene formation. As a result, while triethylamine is commonly used for ketene generation, the majority of the asymmetric catalytic

reactions involving in situ ketene generation from acyl halides substitute *N*,*N*-diisopropylethylamine as the base not only to minimize nucleophilic attack on the acyl halide but also, presumably, to limit amine association with any Lewis acidic reaction addends. Several inorganic base combinations (e.g., NaH/15-crown-5, K_2CO_3) have also been used to integrate acid chloride dehydrohalogenation into asymmetric catalytic cycloadditions.[66]

In the majority of examples, the primary competing reaction is the oligomerization of the ketenes, either thermal or Lewis base accelerated. Obviously, this reaction pathway does not create complications for reactions where the β-lactone ketene dimer is the desired product. However, for reactions requiring the ketene to combine with another reaction component, it is desirable to minimize competing ketene oligomerization. For reactions where the ketene is prepared in advance of the cross-coupling reaction, ketene oligomerization is minimized by keeping the pregenerated ketene solutions at low temperature and by short storage times. For reactions utilizing in situ ketene generation, slow addition of the ketene precursor to a reaction mixture containing the requisite amine base, catalyst, and remaining substrates is most often used to keep the effective ketene concentration low during the cycloaddition event and, thus, minimize ketene dimerization.

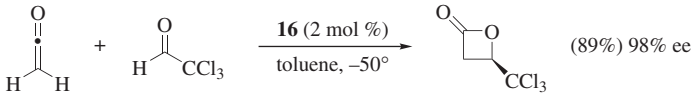
The aldehyde, ketone, and aldimine reaction partners for the ketene cycloadditions are generally stable, easily obtained materials requiring no special precautions for their use in these reactions. However, cycloaddition reactions involving enolizable imine reaction partners are incompatible with using pregenerated, isolated substrates due to the propensity of these compounds to tautomerize to the corresponding enamines. In these cases, in situ imine generation is an effective protocol for minimizing unwanted imine tautomerization relative to the desired ketene–imine cycloaddition reaction. Amine-mediated deprotonation and elimination of α-chloro carbamates and α-amido sulfones each provide a method for in situ imine generation that is compatible with concomitant, in situ ketene generation in catalytic, asymmetric ketene–imine [2 + 2] and [4 + 2] cycloadditions, respectively.[122,124,139]

Enantioenriched cycloaddition catalysts include both Lewis basic and Lewis acidic species. *Cinchona* alkaloid-derived catalysts are, in all cases, stable, isolable species that can be prepared and purified in advance of using them in the cycloaddition reactions. Heterocyclic carbene catalysts are generated in situ during the cycloaddition reaction using the corresponding imidazolium or triazolium salts as carbene precursors and a base (e.g., Cs_2CO_3 or *t*-BuOK) to effect deprotonation of the salt.[241] Chiral Lewis acid catalysts are most often prepared immediately prior to use by ligand exchange of the enantioenriched chelating ligand and an achiral metal alkoxide or metal alkyl species. Thus, Ti(IV)-diol complexes are prepared by reacting the requisite chelating diol with the corresponding Ti(IV) tetra- or dialkoxides. Aluminum(III)-based catalysts are typically generated by the acid–base reaction of the chelating diol or sulfonamide ligand with trialkylaluminum or dialkylaluminum chloride precursors.[96,97,100,101,105,114] In some instances, the enantioenriched Al(III) reaction catalysts are prepared and isolated prior to use in the ketene cycloaddition reactions.[105,116]

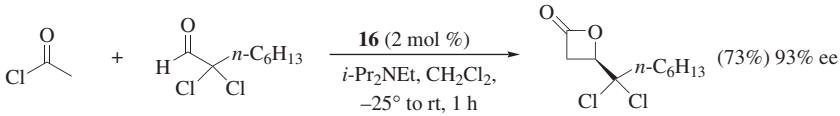
EXPERIMENTAL PROCEDURES

The experimental procedures provided in this section exemplify the reaction protocols described in the text. Many are derived from general procedures described in the primary literature, and, where necessary, weights and volumes of reagents based on equivalency have been added for specific substrates and reagents as an aid to the reader. Before preparing any of the compounds included in this section, the reader should consult the original reference.

EXPERIMENTAL PROCEDURES

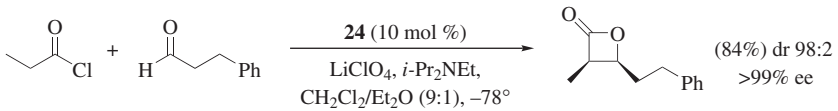


(*R*)-4-Trichloromethyl-2-oxetanone [Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition of an Activated Aldehyde Catalyzed by a *Cinchona* Alkaloid].[64] A three-necked, 100-mL, round-bottomed flask was equipped with a thermometer, a ketene inlet, and a dropping funnel. Toluene (50 mL) was added such that the ketene inlet was below the surface of the toluene. Purified quinidine (**16**, 83 mg, 0.25 mmol) was added and the solution was cooled to −50°. Ketene was prepared by pyrolysis of acetone vapors[238] and was bubbled through the toluene solution with magnetic stirring while anhydrous chloral (1.47 g, 0.01 mol) in toluene (20 mL) was added dropwise over 0.75–1 h. After the reaction was complete, the mixture was warmed to rt and transferred into a separatory funnel. The catalyst was removed by washing twice with 4 N HCl. The toluene layer was washed with sat. aq. NaCl solution and dried over $MgSO_4$. After removing the $MgSO_4$ by filtration, the toluene was evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to afford the title compound (1.67 g, 89%): bp 120° (0.5 mm Hg); $[\alpha]_D^{20}$ − 15.3 (*c* 1, cyclohexane) corresponding to an ee of 98%; NMR δ 5.0 (t, 1H), 3.7 (m, 2H).

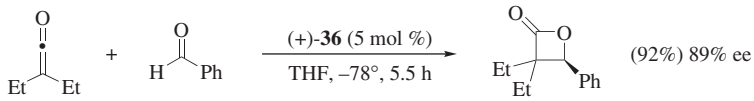


(*R*)-4-(1,1-Dichloroheptyl)-2-oxetanone [*Cinchona* Alkaloid-Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition with Ketene Generated by Amine-Mediated Dehydrohalogenation of Aectyl Chloride].[67] 2,2-Dichlorooctanal (0.50 g, 2.54 mmol, 1.00 equiv) was added to a 25-mL, round-bottomed flask followed by quinidine (**16**, 0.02 g, 0.05 mmol, 0.02 equiv), toluene (3.60 mL), and *N*,*N*-diisopropylethylamine (0.64 mL, 3.68 mmol, 1.45 equiv). The flask was cooled to −25°, and then acetyl chloride (0.18 mL, 2.54 mmol, 1.00 equiv)

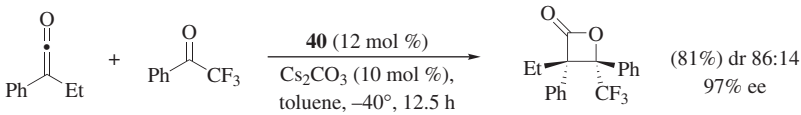
was added dropwise over a 1–2 min period. A precipitate formed immediately. The heterogeneous mixture was stirred for 15 min, and then more acetyl chloride (0.09 mL, 1.27 mmol, 0.50 equiv) was added slowly. The resulting heterogeneous, light-yellow mixture was stirred an additional 45 min at −25° and then warmed to rt. After dilution with 10 mL of Et_2O, the mixture was transferred to a separatory funnel, and additional Et_2O was used to transfer all the solids. The organic layers were washed with 4 N HCl (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography (EtOAc/hexanes = 1:20 to 1:3) to afford the title compound (0.45g, 73%, 93% ee) as a light-yellow oil: GC, T_r (R) = 17.9 ± 0.1 min, T_r (S) = 19.7 ± 0.1 min; R_f0.58 (EtOAc/hexanes = 1:3); $[\alpha]_D^{25}$ + 1.40 (c 4.37, $CHCl_3$); IR (thin film) 1844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (dd, J = 4.2, 5.7 Hz, 1H), 3.70 (dd, J = 3.9, 16.8 Hz, 1H), 3.62 (dd, J = 5.7, 16.8 Hz, 1H), 2.32–2.11 (m, 2H), 1.79–1.59 (m, 2H), 1.40–1.29 (m, 6H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 91.7, 72.3, 43.9, 41.6, 31.3, 28.4, 24.3, 22.3, 13.8; HRMS–FAB (m/z): $[M + H]^+$ calcd for $C_{10}H_{17}Cl_2O_2$, 239.0606; found, 239.0606.



(3*R*,4*S*)-3-Methyl-4-(2-phenylethyl)oxetan-2-one [Lewis Acid Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition].[72] To a solution of *O*-trimethylsilylquinine (**24**, 40 mg, 0.10 mmol, 10 mol %) and $LiClO_4$ (53 mg, 0.5 mmol, 50 mol %) in Et_2O (1.0 mL) was added CH_2Cl_2 (2.0 mL) and the reaction mixture was cooled to −78°. To the resulting mixture was added *N*,*N*-diisopropylethylamine (0.44 mL, 2.5 mmol) followed by hydrocinnamaldehyde (0.13 mL, 1.0 mmol). A solution of propianoyl chloride (0.17 mL, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was then added over 1 h by syringe pump. The reaction mixture was stirred for 7 h, quenched at −78° with Et_2O (10 mL), and the resulting mixture was filtered through silica gel eluting with Et_2O (3 × 20 mL). The filtrate was concentrated under vacuum and the crude product mixture was purified by flash chromatography (10% EtOAc in hexane) to give the title compound (161 mg, 84%) as a colorless oil. Separation of enantiomers by chiral HPLC [(Daicel Chiracel™ OD-H column, 1.0 mL/min, 2-propanol/hexane = 5:95) T_r (3*S*,4*R*) = 12.9 min, T_r (3*R*,4*S*) = 14.0 min] provided only one enantiomer (3*R*,4*S*) (>99% ee): $[\alpha]_D$ − 47.2 (c 2.04, $CHCl_3$); IR (thin film) 1821, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.59 (ddd, J = 10.5, 6.4, 4.1 Hz, 1H), 3.76 (qd, J = 7.8, 6.5 Hz, 1H), 2.90 (ddd, J = 13.8, 9.4, 5.3 Hz, 1H), 2.72 (ddd, J = 13.8, 8.8, 7.5 Hz, 1H), 2.13–1.97 (m, 2H), 1.29 (d, J = 7.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 140.4, 128.6, 128.4, 126.4, 74.6, 47.2, 31.9, 31.5, 8.1; HRMS (m/z): M^+ calcd for $C_{12}H_{14}O_2$, 190.0994; found, 190.0990.

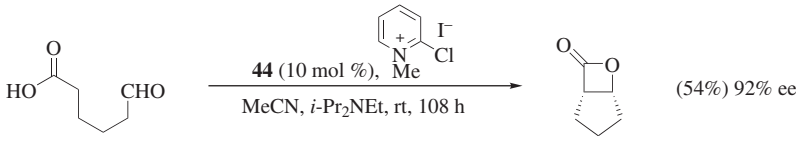


(*S*)-3,3-Diethyl-4-phenyloxetan-2-one [Fe(II)-Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition].[79] A solution of 4-(pyrrolidino)pyridine complex (+)-**36** (6.0 mg, 0.016 mmol) in THF (0.40 mL) was added dropwise over 5 min to a −78° solution of diethylketene (38 mg, 0.38 mmol) and benzaldehyde (32 μL, 0.32 mmol) in THF (1.5 mL). The reaction mixture was stirred at −78° for 5.5 h and then filtered through a short pad of silica gel with copious washings using Et_2O. The solvent was removed, and the product was purified by silica gel chromatography (Et_2O/pentane = 1:9), which furnished the title compound (61 mg, 92%) as a clear oil: HPLC (Daicel Chiralcel AD column, 1.0 mL/min, 2-propanol/hexanes = 3.5:96.5) T_r (minor) = 6.4 min, T_r (major) = 7.4 min, 89% ee; $[\alpha]_D^{21.6}$ + 62 (*c* 0.19, CH_2Cl_2; FTIR (NaCl) 1824, 1454, 1248, 1102, 942 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.24 (m, 5H), 5.38 (s, 1H), 1.98 (m, 2H), 1.48–1.36 (m, 1H), 1.31–1.19 (m, 1H), 1.13 (t, J = 7.5 Hz, 3H), 0.77 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.3, 135.4, 128.7, 128.5, 125.7, 80.9, 64.5, 24.7, 21.9, 8.7, 7.9; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_{16}NaO_2$, 227.1048; found 227.1046.

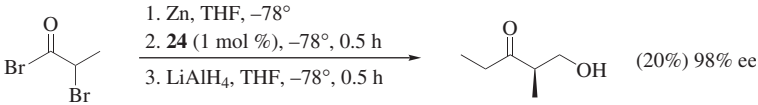


(3*S*,4*S*)-3-Ethyl-3,4-diphenyl-4-(trifluoromethyl)oxetan-2-one [Heterocyclic Carbene-Catalyzed Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition of a Trifluoromethyl Ketone].[80] To an oven-dried, 50-mL reaction tube containing a stir bar was added triazolium salt **40** (73.4 mg, 0.12 mmol), Cs_2CO_3 (32.6 mg, 0.10 mmol), and toluene (5 mL). The reaction mixture was stirred under N_2 for 1.0 h at rt, and then cooled to −40°. 2,2,2-Trifluoroacetophenone (0.14 mL, 1.0 mmol) was added via syringe followed by ethylphenylketene (0.23 mL, 1.5 mmol) and the reaction mixture was stirred at −40° for 12.5 h. The reaction was quenched by the addition of silica gel and the mixture was further stirred for 5 min. The reaction mixture was diluted with EtOAc, filtered through a pad of silica gel, and washed with EtOAc. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether/Et_2O = 90:1) to give the title compound (259 mg, 81%): mp: 57–58°; $[\alpha]_D^{20}$ + 31.8 (*c* 1.2, $CHCl_3$); $[\alpha]_D^{20}$ + 34.3 (*c* 1.1, $CHCl_3$, for the pure *trans*-isomer after recrystallization from Et_2O/*n*-hexane); GC (CP-Chirasil-DexCB #CP7502 column, 10 psi/min, split ratio = 80, column oven = 150°) T_r (minor) 28.5 min, T_r (major) 29.3, 97% ee; IR (KBr) 3065, 2979, 1844, 1496, 1451, 1299, 1172, 1022, 964, 938, 768, 710 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) (*trans*) δ 7.22–6.97 (m, 10H), 2.86–2.74 (m, 1H), 2.51–2.39 (m, 1H), 0.92 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (*trans*) δ 169.6, 132.8, 131.4, 129.7, 128.7, 128.4, 127.9, 127.5, 126.1, 124.1 (q, $J = 282.0$ Hz), 84.8 (q, $J = 31.1$ Hz), 75.1, 24.8 (q, $J = 3.3$ Hz), 9.8; EIMS (m/z): M^+ 320, 276, 146 (100), 118 (65.0), 117 (92.8), 103 (41.3); HRMS–EI (m/z): M^+ calcd for $C_{18}H_{15}F_3O_2$, 320.1024; found, 320.1027. Anal. Calcd for $C_{18}H_{15}F_3O_2$: C, 67.50; H, 4.72. Found: C, 67.52; H, 4.80.

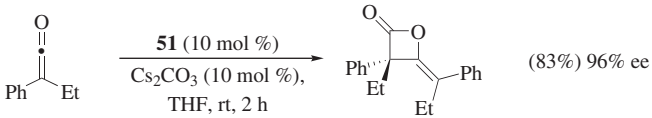


(1*R*,2*S*)-6-Oxabicyclo[3.2.0]heptan-7-one [Intramolecular Asymmetric [2 + 2] Ketene–Carbonyl Cycloaddition].[81] *O*-Acetylquinidine (**44**) (136 mg, 0.384 mmol), *N*-methyl-2-chloropyridinium iodide (2.95 g, 11.53 mmol), and *N*,*N*-diisopropylethylamine (2.70 mL, 15.4 mmol) were placed in a 100-mL, round-bottomed flask containing MeCN (45 mL). To this slurry was added a solution of 6-oxohexanoic acid (500 mg, 3.84 mmol) in MeCN (32 mL) via syringe pump over 12 h. After the addition was complete, the reaction mixture was stirred an additional 96 h at rt. The solvent was removed under vacuum and the orange residue was partitioned between Et_2O (100 mL) and water (100 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with sat. aq. NH_4Cl solution (3 × 200 mL), and then brine (1 × 200 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on SiO_2 (Et_2O/hexanes = 1:1 to 1:0) to give the title compound (233 mg, 54%) as a light yellow oil: chiral GC (2,3-diacetoxy-6-(*t*-butyl)dimethylsilyl β-cyclodextrin column, 130°, 11 psi) T_r (1*S*,2*R*) (minor) = 20.68 min, T_r (1*R*,2*S*) (major) = 21.32 min, 92% ee; $[\alpha]_D^{25} + 85.0$ (*c* 0.02, MeOH); IR (thin film) 1818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$). δ 5.00 (app t, $J = 3.9$ Hz, 1H), 3.90 (dd, $J = 3.9$, 7.8 Hz, 1H), 2.20 (dd, $J = 6.3$, 14.4 Hz, 1H), 2.13 (dd, $J = 7.2$, 12.6 Hz, 1H), 1.98–1.89 (m, 1H), 1.85–1.69 (m, 1H), 1.65–1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$). δ 171.3, 77.4, 55.5, 30.5, 26.1, 22.0; HRMS–FAB (m/z): $[M + H]^+$ calcd for $C_{13}H_{18}NO_3$ (benzyl hydroxamic acid derivative), 236.1287; found, 236.1277.



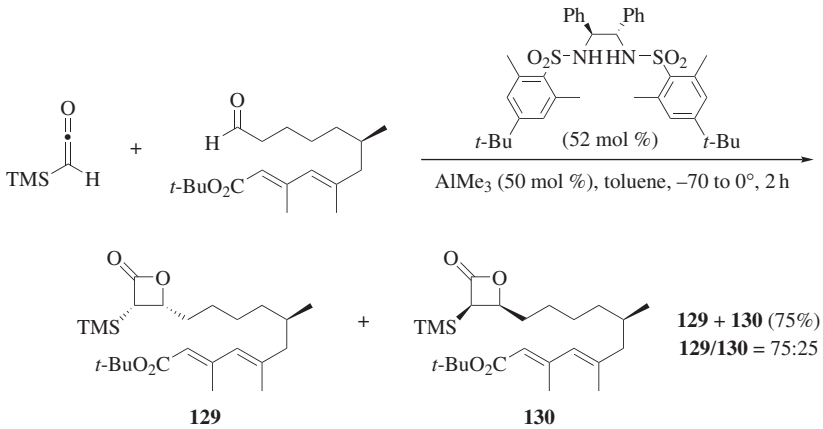
(*R*)-1-Hydroxy-2-methyl-3-pentanone [Catalytic Asymmetric Ketene Dimerization–$LiAlH_4$ Reduction].[84] Zinc powder (1.57 g, 24.0 mmol) was suspended in THF (5 mL) in a 50-mL distillation flask attached to a short-path

distillation apparatus. The pressure in the system was adjusted to 100 mmHg, whereupon the solvent began to mildly reflux. A solution of 2-bromopropionyl bromide (2.16 g, 10.0 mmol) in THF (7 mL) was added via a Teflon cannula at such a rate as to maintain vigorous gas evolution. Methylketene was collected as a THF solution in a 50-mL receiver flask cooled to 77 K. After the addition of 2-bromopropianoyl bromide was completed, the receiving flask was removed from the distillation apparatus, placed under N_2, and warmed to −78°, upon which the reaction mixture became a lime-green solution. This solution was added over 5 min via an insulated Teflon cannula to a solution of *O*-trimethylsilylquinidine (**24**) (11.90 mg, 0.0300 mmol) in THF (5 mL), resulting in a clear, colorless solution. After 0.5 h at −78°, $LiAlH_4$ (1.0 M in Et_2O, 1.00 mL, 1.00 mmol) was added. The resulting solution was stirred for 0.5 h at −78° and then quenched with MeOH (0.6 mL). The mixture was warmed to rt and the solvents were removed under vacuum. The residue was partitioned between CH_2Cl_2 (10 mL) and an HCl solution (1 M, 10 mL) that had been saturated with NaCl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1 × 15 cm, step gradient from 2.5% to 12.5% EtOAc in hexanes, 2.5% steps) yielded the title compound (0.116 g, 20%) as a clear, colorless oil: $[\alpha]_D$ − 19.3 (c 0.85, $CHCl_3$) [lit.[84] $[\alpha]_D$ − 22 (c 0.85, $CHCl_3$)]; IR (thin film) 3440, 1709 cm^{-1}; ^1H NMR ($CDC1_3$–D_2O) δ 3.74, 3.65 (ABX, $J_{AB} = 11.1$, $J_{AX} = 7.4$, $J_{BX} = 4.3$ Hz, 2H), 2.77 (pent d, $J = 7.3$, 4.3 Hz, 1H), 2.59, 2.48 (ABX, $J_{AB} = 18.0$, $J_{AX} = J_{BX} = 7.3$ Hz, 2H), 1.13 (d, $J = 7.3$ Hz, 3H), 1.06 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR δ 215.5, 64.2, 47.7, 34.7, 13.2, 7.3. Anal. Calcd for $C_6H_{12}O_2$ (1.54% H_2O present): C, 61.09; H, 10.43. Found: C, 61.26; H, 10.07.



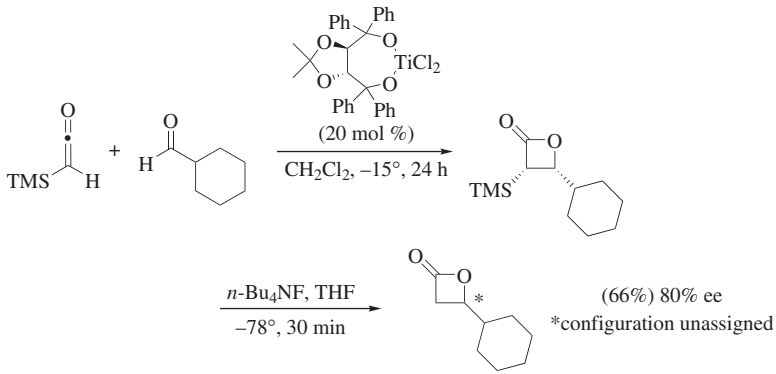
(*S,Z*)-3-Ethyl-3-phenyl-4-(1-phenylpropylidene)oxetan-2-one [Heterocyclic Carbene-Catalyzed Asymmetric Dimerization of an Alkyl Aryl Ketene].[89] The triazolium salt **51** (76 mg, 0.1 mmol) and Cs_2CO_3 (32.6 mg, 0.1 mmol) were dissolved in THF (4 mL) and the resulting mixture was stirred at rt for 30 min. Ethylphenylketene (0.15 mL, 1 mmol) was added and the reaction mixture was stirred at rt for 2 h. The mixture was then filtered through a pad of silica gel and washed with EtOAc. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 30:1) to give the title compound (129 mg, 83%) as a colorless oil: HPLC (Daicel Chiralpak AD-H column, 20°, 0.5 mL/min, 2-propanol/hexane = 5:95) T_r (minor): 8.6 min, T_r (major) 10.3 min, 96% ee; $[\alpha]_D^{25}$ − 23.7 (*c* 2.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.17 (m, 10H), 2.34–2.23 (m, 3H), 2.22–2.05 (m, 1H), 1.13 (t, $J = 7.5$ Hz, 3H), 0.81

(t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 143.9, 135.3, 134.6, 129.2, 128.5, 128.5, 128.1, 127.5, 126.4, 116.4, 70.0, 26.2, 22.8, 12.7, 9.9; IR (KBr, film) 2969, 1857, 1140, 914, 889, 696 cm^{-1}; HRMS–EI (m/z): M$^+$ calcd for $C_{20}H_{20}O_2$, 292.1463; found, 292.1467.



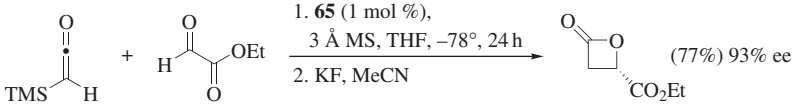
***tert*-Butyl (*R*,2*E*,4*E*)-3,5,7-Trimethyl-11-[(2*R*,3*S*)-4-oxo-3-(trimethylsilyl) oxetan-2-yl]undeca-2,4-dienoate (129) and *tert*-Butyl (*R*,2*E*,4*E*)-3,5,7-Trimethyl-11-[(2*S*,3*R*)-4-oxo-3-(trimethylsilyl)oxetan-2-yl]undeca-2,4-dienoate (130) [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Amine Complex; AAC Reaction].[99]** To a solution of (*S*,*S*)-*N*,*N*′-bis(4-*tert*-butyl-2,6-dimethyphenylsulfonyl)-1,2-diphenylethylene-1,2-diamine (342 mg, 0.517 mmol) in toluene (20 mL) was added Me_3Al in toluene (2.0 M, 0.25 mL, 0.50 mmol). The reaction mixture was stirred at rt for 10 min then cooled to −70°, whereupon the aldehyde (304 mg, 0.985 mmol) in toluene (5 mL + 2 × 1 mL rinses) was added dropwise. The mixture was stirred for 5 min then trimethylsilylketene (146 mg, 1.28 mmol) in toluene (5 mL) was added dropwise. The mixture was stirred, warming to 0° over 2 h when it was quenched with sat. aq NH_4Cl (5 mL). The resulting mixture was diluted with Et_2O (20 mL) and the layers were shaken and separated. The aqueous portion was extracted with Et_2O (20 mL) and the combined organic extracts were washed with 1 N HCl (10 mL) and brine (20 mL) and then dried, filtered, and concentrated. The resulting colorless oil was chromatographed (silica gel, hexanes/Et_2O = 95:5 to 80:20) to yield a mixture of the title compounds (279 mg, 67%; **129/130** = 3:1) and another fraction containing a **129/130** mixture (1.3:1, 32 mg, 8%), each as a colorless oil. The NMR spectra for the **129/130** mixture indicated a single compound; therefore the diastereomer ratio was determined by recording the spectra in the presence of (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol where the doublets ($J = 6.1$ Hz) arising from the C3′ methine signals were clearly distinguishable (**129** δ = 3.31 and **130** δ = 3.30). The total yield of the β-lactones **129** and **130** (*cis/trans* 94:6) was 75%: $[\alpha]_D + 17.1$ (*c* 2.765, $CHCl_3$); IR (film)

2929s, 2862s, 1805s, 1705s, 1623s, 1456s, 1390s, 1367s, 1332m, 1292s, 1253s, 1141s, 1004m, 913m, 847s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.63 (br s, C2*H*, 1H), 5.54 (m, C4*H*, 1H), 4.54 (ddd, $J = 9.2$, 6.1, 4.8 Hz, C2′*H*, 1H), 3.31 (d, $J = 6.1$ Hz, C3′*H*, 1H), 2.16 (d, $J = 1.2$ Hz, C3*Me*, 3H), 2.03 (dd, $J = 12.8$, 6.6 Hz, C6$H_A H_B$, 1H), 1.80 (dd, $J = 12.8$, 7.8 Hz, C6$H_A H_B$, 1H), 1.75 (d, $J = 1.2$ Hz, C5*Me*, 3H), 1.45 (s, CMe_3, 9H), 1.6–1.0 (m, 9H), 0.80 (d, $J = 6.5$ Hz, C7*Me*, 3H), 0.20 (s, Me_3Si, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.0, 166.8, 152.7, 140.4, 129.7, 119.4, 79.6, 74.1, 49.0, 46.4, 36.7, 33.6, 30.9, 28.4, 26.7, 19.5, 19.4, 18.4, −1.0; LRMS–CI (NH_3) (m/z): $[M + H]^+$423, 367, 349. Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.43; H, 9.97.

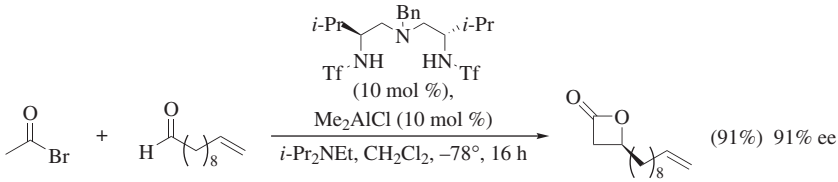


4-Cyclohexyloxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of the Ti(IV)–TADDOL Complex].[102] The chiral Ti(IV)-diol complex obtained from [(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]bis(diphenylmethanol) was prepared as a stock solution (0.40 M) in CH_2C1_2 immediately prior to use by the procedure of Corey.[242] To a solution of cyclohexanecarboxaldehyde (101.7 mg, 0.89 mmol) and trimethylsilylketene (204.8 mg, 1.79 mmol) in CH_2Cl_2 (1 mL) was added the stock solution of Ti(IV)–TADDOL complex (0.44 mL, 0.18 mmol) at −20°. The resulting reaction mixture was kept in a freezer (−15°) for 24 h. After addition of pH 7 buffer (1 mL) at −20°, the reaction mixture was warmed to rt and filtered through Celite. The solution was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a pasty colorless solid which was roughly purified using flash chromatography (EtOAc/hexanes = 1:9) to remove polar impurities. The purified 3-trimethylsilyl-4-cyclohexyloxetan-2-one was treated with TBAF (1 M in THF, 0.98 mL, 0.98 mmol) at −78°. After stirring for 30 min, the reaction mixture was quenched with pH 7 buffer, extracted with Et_2O, dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by flash chromatography (EtOAc/hexanes = 1:10) to afford the title compound (90.5 mg, 66%): chiral stationary phase GC [bis(*t*-butyldimethylsilyl)cyclodextrin] 80% ee; R_f0.32 (EtOAc/hexanes = 1:9); IR (thin film) 2929, 1832 cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$). δ 4.25–4.15 (m, 1H), 3.43 (dd, $J = 5.8$, 16.3 Hz, 1H), 3.11 (dd, $J = 4.4$, 16.3 Hz, 1H), 1.97–1.52 (m, 6H), 1.39–0.90 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$). δ 168.5, 74.7, 41.7, 40.7, 27.9, 26.9, 25.7, 25.1, 24.9; HRMS–FAB (m/z): $[M + H]^+$ calcd for $C_9H_{14}O_2$, 155.1072; found, 155.1081. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.34; H, 9.22.

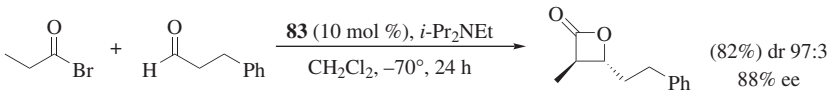


(2*S*)-4-Oxo-oxetane-2-carboxylic Acid Ethyl Ester [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of Cu(II)–Bis(oxazoline) Complex].[104] A dry flask was charged with $[Cu\{(S,S)\text{-t-Bu-box}\}(H_2O)_2(OTf)][OTf]$ (**65**, 6.7 mg, 0.01 mmol) and powdered 3 Å molecular sieves (8 mg, dried at 300° for 24 h). The flask was fitted with a septum and THF (10 mL) was added via syringe. The mixture was stirred for 30 min, cooled to −78° and treated with freshly distilled ethyl glyoxalate (128 μL, 1 equiv, 1.0 mmol) followed by addition of trimethylsilylketene (155 μL, 126 mg, 1.1 equiv, 10 mmol). After 24 h at −78° the reaction mixture was filtered through a plug of SiO_2 and concentrated under vacuum. To the silylated intermediate in MeCN (1 mL) was added KF (120 mg, 1.0 equiv., 2.0 mmol). After 20 min at rt, the solution was filtered through a plug of florisil and SiO_2. Concentration under vacuum provided the pure title compound (111 mg, 77%). (If required, the product may be purified by flash chromatography on silica gel eluting with Et_2O/hexanes = 30:70). GC (Cyclodex β, 80–95°, 0.5°/min, 5 min initial, 25 psi) T_r (major) = 19.9 min, T_r (minor) = 20.4 min, 93% ee; $[\alpha]_D^{25} - 8.3$ (c 0.75, $CHCl_3$); IR (film) 3026, 1846, 1749, 1215, 759, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (dd, $J = 6.5$, 4.5 Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 1H), 3.78 (dd, $J = 16.5$, 6.5 Hz, 1H), 3.61 (dd, $J = 16.5$, 4.5 Hz, 1H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 165.7, 65.3, 62.5, 43.5, 14.1; HRMS–EI (m/z): $[M + H]^+$ calcd for $C_6H_8O_4$, 145.0501; found, 145.0506.



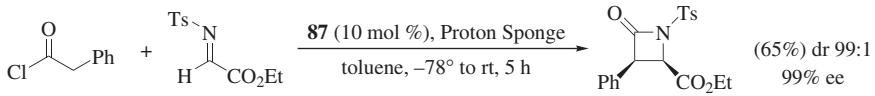
(*S*)-4-(9-Decylenyl)oxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Bis(sulfonamide) Complex].[105] To a solution of (2*S*,6*S*)-4-benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane (54 mg, 0.10 mmol) in CH_2Cl_2 (8 mL)

at rt was added a solution of Me_2AlCl (100 μL, 1 M in hexanes, 0.1 mmol) via syringe. The resulting homogeneous colorless solution was stirred at rt for 1 h, whereupon *N*,*N*-diisopropylethylamine (296 μL, 1.7 mmol) was added via syringe. The reaction was cooled to −50° and acetyl bromide (140 μL, 1.9 mmol) and undecylenic aldehyde (210 μL, 1.0 mmol) were added via syringe. The mixture was stirred for 16 h until the reaction was complete as monitored by TLC. The reaction mixture was eluted through a silica gel pad with CH_2Cl_2 and the filtrate was concentrated under vacuum. Purification by flash chromatography (EtOAc/hexanes = 4:96) gave the title compound (191 mg, 91%): chiral GLC (Chiraldex™ G-TA column, flow rate 0.5 mL/min, 100° for 10.00 min, ramp @ 5.0°/min to 130° for 12.00 min, ramp @ 10.0°/min to 160° for 15.00 min) T_r (*R*) = 38.5 min, T_r (*S*) = 39.7 min, 4(*S*)/4(*R*) = 95.5:4.5, 91% ee; $[\alpha]_D$ − 20.2 (*c* 4.7, CH_2Cl_2); IR (NaCl) 3075, 1828, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85–5.76 (m, 1H), 5.02–4.90 (m, 2H), 4.52–4.46 (m, 1H), 3.50 (dd, *J* = 16.2, 5.6 Hz, 1H), 3.05 (dd, *J* = 16.2, 4.3 Hz, 1H), 2.05–2.00 (m, 2H), 1.86–1.73 (m, 2H), 1.45–1.29 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 139.2, 114.3, 71.4, 43.0, 34.8, 33.8, 29.4 (2C), 29.2, 29.1, 29.0, 25.0; EIMS (70 eV) (*m*/*z*): 167, 150, 135, 121, 109, 95, 81, 67; HRMS (*m*/*z*): M^+ calcd for $C_{13}H_{22}O_2$, 210.1620; found, 210.1626.

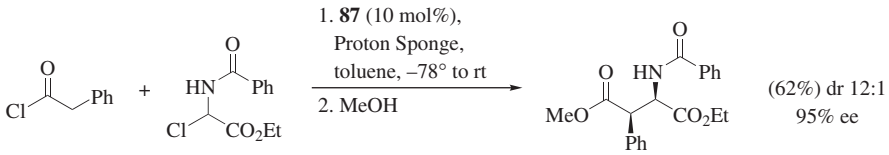


(3*R*,4*R*)-3-Methyl-4-(2-phenylethyl)oxetan-2-one [Lewis Acid Catalyzed [2 + 2] Ketene–Carbonyl Cycloaddition in the Presence of an Al(III)–Salen Complex].[116] To a mixture of complex **83** (61.4 mg, 0.075 mmol, 0.1 equiv) in CH_2Cl_2 (3 mL) was successively added at −70°, 3-phenylpropanal (66 μL, 0.50 mmol), propionyl bromide (405 μL, 4.5 mmol, 9 equiv) and *N*,*N*-diisopropylethylamine (326 μL, 1.875 mmol, 2.5 equiv). The resulting heterogeneous mixture was stirred at −70° for 24 h. The reaction mixture was poured into aq 1 M HCl (30 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried over $MgSO_4$ and filtered through a short plug of silica gel. CH_2Cl_2 was subsequently removed under vacuum to yield the title compound (82%, 88% ee, dr 97:3). The yield was determined by ^1H-NMR spectroscopy using acetophenone as an internal standard. The diastereomer ratio was also determined by ^1H-NMR, whereas the enantiomeric composition ee was determined by HPLC (Chiralcel OD-H, 210 nm, 1.0 mL/min, *n*-hexane/2-propanol = 97:3). An analytically pure sample was obtained as a colorless oil by flash chromatography (pentane/Et_2O = 20:1): $[\alpha]_D^{25.9}$ + 67.4 (*c* 1.280, $CHCl_3$); FTIR 2935, 1816, 1603, 1124, 840, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.17 (m, C*H*Ar, 5H), 4.16 (ddd, *J* = 7.5, 5.9, 4.0, C*H*O, 1H), 3.20 (qd, *J* = 7.5, 4.0, C*H*C(O), 1H), 2.77 (m, CH_2CH_2CAr, 2H), 2.13 (m, CH_2CH_2CAr, 2H), 1.32 (d, *J* = 7.5, CH_3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 139.9, 128.5, 128.2, 126.3, 78.6,

50.8, 35.6, 31.4, 12.5; HRMS–EI (m/z): M^+ calcd for $C_{12}H_{14}O_2$, 190.0994; found, 190.0989. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.85; H, 7.53.

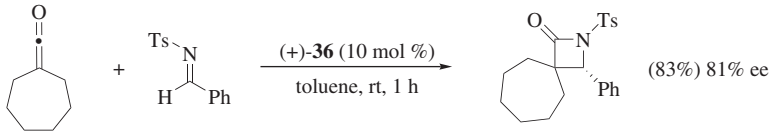


Ethyl (2*R*,3*R*)-4-Oxo-3-phenyl-1-tosylazetidine-2-carboxylate [Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloaddition in the Presence of a *Cinchona* Alkaloid Catalyst].[66,118] To a solution of phenylacetyl chloride (20 mg, 0.129 mmol, 1.0 equiv) in toluene (0.5 mL) at −78° was added Proton Sponge (31 mg, 0.142 mmol, 1.1 equiv) in toluene (0.5 mL) immediately followed by *O*-benzoylquinine (**87**) (6 mg, 0.0129 mmol, 0.1 equiv) and the α-imino ester (33 mg, 0.129 mmol, 1.0 equiv). The reaction mixture was stirred for 5 h as it slowly warmed to rt. The reaction was quenched with MeOH (0.5 mL) and the solvent was removed under reduced pressure. The crude mixture was subjected to column chromatography (EtOAc/hexanes = 15:85) on a plug of silica gel (1.0 cm x 5 cm) yielding the title compound (32 mg, 65%): HPLC [CH_2Cl_2/0.5% HOAc/hexanes = 15:85, 1.0 mL/min] T_r (R,R) = 10.56 min, T_r (R,S) = 8.23 min, T_r (S,R) = 14.17 min, T_r (S,S) = 18.75 min; mp 109−112° (Et_2O/hexanes); $[\alpha]_D$ − 21.1 (c 0.0075, CH_2Cl_2); IR (CH_2Cl_2) 3021, 2963, 1800, 1751, 1369, 1263, 1217, 1171, 1090, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, 2H), 7.40 (d, 2H), 7.27 (m, 3H), 7.10 (m, 2H), 4.99 (d, 1H), 4.89 (d, 1H), 7.48 (m, 2H), 2.48 (s, 3H), 0.75 (t, 3H); ^{13}C NMR ($CDC1_3$) δ 130.2, 129.3, 129.2, 129.1, 128.4, 105.2, 88.6, 87.5, 62.1, 59.6, 58.6, 30.0, 22.2, 13.8, 8.2.

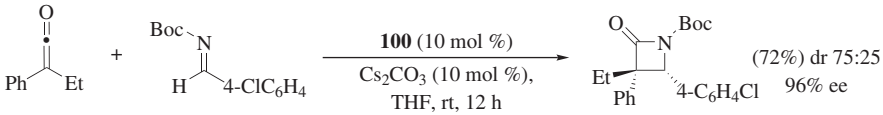


1-Ethyl 4-Methyl (2*R*,3*R*)-2-Benzamido-3-phenylsuccinate [Lewis Base Catalyzed [2 + 2] Ketene–Imine Cycloaddition–Solvolysis].[123,124] A 25-mL round-bottomed flask equipped with a stir bar was loaded under N_2 with ethyl 2-benzamido-2-chloroacetate (63 mg, 0.26 mmol), Proton Sponge (83 mg, 0.39 mmol), and *O*-benzoylquinine (**87**) (6 mg, 0.013 mmol). Toluene (1 mL) was added and the mixture was stirred for 1 h. The solution was diluted with toluene (7 mL) and cooled to −78° in a dry ice/acetone bath. Phenylacetyl chloride (20 mg, 0.13 mmol) in toluene (1 mL) was added dropwise. The mixture was allowed to slowly warm to rt overnight. Excess methanol (6 mL) was added, and the solution was heated at reflux. The reaction was monitored by TLC and stopped when all of the β-lactam had reacted (∼4 h). The solvent was removed

under vacuum, and the residue was dissolved in $CHCl_3$ (10 mL) and washed with 1 M HCl (3 × 10 mL). The organic layer was dried with $MgSO_4$ and filtered through Celite. The filtrate was concentrated and the residue was submitted to flash column chromatography to yield the title compound (22 mg, 62%, 95% ee): HPLC [2-propanol/1.0% HOAc/hexanes = 5:95, 1.0 mL/min] T_r (*R*,*R*) = 64.2 min, T_r (*R*,*S*) = 59.3 min, T_r (*S*,*R*) = 69.1 min, T_r (*S*,*S*) = 72.8 min; mp 149–150° (Et_2O/hexanes); $[\alpha]_D + 6.5$ (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 1222, 1377, 1463, 1508, 1674, 1741, 2157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84–7.79 (m, 2H), 7.58–7.41 (m, 4H), 6.95 (br d, 1H), 6.83 (dd, 4H), 5.48 (dd, 1H), 5.19 (d, 1H), 4.10 (qt, 2H), 3.75 (s, 3H), 1.22 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 171.5, 168.1, 135.4, 132.8, 131.8, 130.3, 130.0, 129.8, 129.5, 128.3, 67.0, 56.1, 53.9, 53.2, 15.1. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.5; H, 5.96; N, 3.94. Found C, 67.5; H, 5.97; N, 3.96.

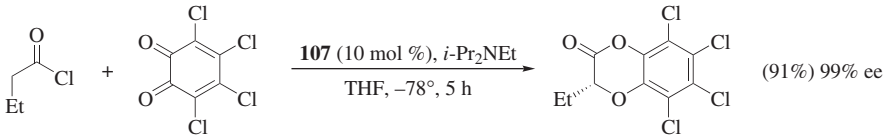


(*S*)-3-Phenyl-2-tosyl-2-azaspiro[3,6]decane-1-one [Fe(II)–Azaindene-Catalyzed [2 + 2] Ketene–Imine Cycloaddition].[126] In a nitrogen-filled glove box, a solution of hexamethyleneketene (22.2 mL, 0.154 mmol) and *N*-benzylidene-4-methylbenzenesulfonamide (45.9 mg, 0.177 mmol) in toluene (2.0 mL) was added to 4-(pyrrolidino)pyridine complex (+)-**36** (0.10 equiv, 5.8 mg, 0.015 mmol) in toluene (3.6 mL). The reaction mixture was stirred at rt for 1 h and then purified directly by flash chromatography (SiO_2, 25–50% Et_2O/hexanes) to afford the title compound (49.1 mg, 83%) as a white solid: HPLC (Daicel Chiralcel OD column, 1.0 mL/min, 2-propanol/hexanes = 10:90) T_r (major) = 7.3 min, T_r (minor) = 9.9 min, 81% ee; mp 110–112°; $[\alpha]_D^{20} - 126$ (c = 1.0, CH_2Cl_2); FTIR (NaCl) 2928, 2857, 1789, 1597, 1496, 1456, 1366, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7, 2H), 7.32 (m, 5H), 7.19 (m, 2H), 4.75 (s, 1H), 2.47 (s, 3H), 1.88–1.70 (m, 3H), 1.50 (m, 4H), 1.38–1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 145.4, 135.6, 134.8, 130.1, 128.7, 128.6, 127.8, 127.2, 70.0, 63.7, 35.2, 30.1, 29.3, 29.2, 23.7, 22.9, 22.0; HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{26}NO_3S$, 384.1628; found, 384.1636.

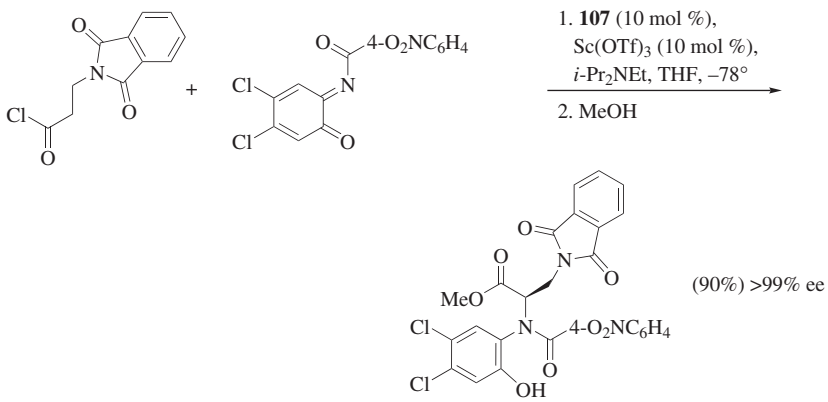


(3*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-3-ethyl-4-(4-chlorophenyl)-3-phenylazetidin-2-one [Heterocyclic Carbene-Catalyzed [2 + 2] Ketene–Imine

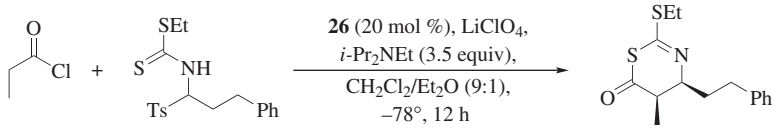
Cycloaddition].[129] To a mixture of *tert*-butyl (*E*)-(4-chlorobenzylidene)carbamate (119.8 mg, 0.5 mmol) and triazolium salt **100** (28.4 mg, 0.05 mmol) in THF (2.5 ml), ethylphenylketene (92 μL, 0.6 mmol) and Cs_2CO_3 (16.3 mg, 0.05) were added. The reaction mixture was stirred under N_2 at rt until TLC indicated complete consumption of the imine (12 h). The solvent was removed under reduced pressure and a small portion of sample was collected to determine the *cis/trans* ratio of the β-lactams by ^{1}H NMR. The remainder was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 7:3) to give the title compound as a white solid (72%): HPLC (Daicel Chiralpak AD-H column, 20°, 1.0 mL/min, 2-propanol/hexanes = 2:98) T_r (minor) = 7.2 min, T_r (major) = 12.2 min, 96% ee (*cis*); mp 169–170°; $[\alpha]_D^{25}$ − 83.7 (*c* 0.5, CH_2Cl_2); IR (KBr) 2977, 1792, 1707, 1349, 1157, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3) δ 7.10–7.08 (m, 5H), 6.99–6.96 (m, 2H), 6.88 (d, J = 8.1 Hz, 2H), 4.92 (s, 1H), 2.30–2.20 (m, 2H), 1.39 (s, 9H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 168.6, 147.7, 135.0, 134.6, 133.7, 128.5, 128.2, 128.1, 127.5, 127.1, 83.6, 69.0, 65.6, 32.2, 27.9, 9.4; HRMS–P-SIMS (m/z): $[M + H]^+$ calcd for $C_{22}H_{25}ClNO_3$, 386.1523; found, 386.1517.



(*R*)-5,6,7,8-Tetrachloro-3-ethylbenzo[*b*][1,4]dioxin-2(3*H*)-one [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene–Benzoquinone Cycloaddition].[134] *O*-Benzoylquinidine (**107**) (23.6 mg, 0.055 mmol) was added to a 25-mL, round-bottomed flask equipped with a magnetic stir bar and dissolved in THF (3 mL). The flask was cooled to −78° and *N*,*N*-diisopropylethylamine (96 μL, 0.55 mmol) was added followed by *o*-chloranil (135 mg, 0.55 mmol) as a solution in THF (4 mL). Butanoyl chloride (57 μL, 0.55 mmol), as a solution in THF (3 mL), was then added to the reaction mixture. The reaction was monitored by TLC and stopped once all of the quinone was consumed (about 5 h). The reaction mixture was filtered through a plug of silica gel, and the plug was flushed thoroughly with hexanes. Concentration of the filtrate under vacuum yielded the title compound as a white crystalline solid (91%): HPLC (Chiracel OD, 2-propanol/hexanes = 7:93, 1.0 mL/min) T_r (*S*) = 6.95 min, T_r (*R*) = 7.34 min, 99% ee; mp 120–122°; $[\alpha]_D$ + 7.3 (*c* 0.005, $CHCl_3$); IR (CH_2Cl_2)1778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.65 (m, 1H), 2.01 (m, 2H), 1.17 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 161.9, 138.7, 137.7, 129.0, 127.1, 121.5, 120.6, 60.3, 23.8, 9.18. Anal. Calcd for $C_{10}H_6Cl_4O_3$: C, 38.0; H, 1.91. Found C, 37.8; H, 1.92.

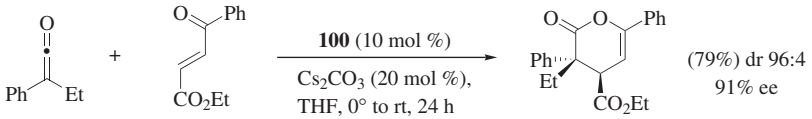


Methyl (*R*)-2-(*N*-(4,5-Dichloro-2-hydroxyphenyl)-4-nitrobenzamido)-3-(1,3-dioxoisoindolin-2-yl)propanoate [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene–Quinone Imine Cycloaddition].[137] A solution of the quinone imine, (*E*)-*N*-(3,4-dichloro-6-oxocyclohexa-2,4-dien-1-ylidene)-4-nitrobenzamide (39.0 mg, 0.12 mmol) in THF (1 mL), was added dropwise at −78° to a reaction flask containing *O*-benzoylquinidine (**107**) (5.1 mg, 0.012 mmol), scandium(III) triflate (5.9 mg, 0.012 mmol), *N*,*N*-diisopropylethylamine (21 μL, 0.12 mmol), and 1-(2-phthalimidopropiano)chloride (28.5 mg, 0.12 mmol) in THF (3 mL). The mixture was stirred at −78° and monitored by TLC. When the reaction was complete, it was quenched with methanol (3 mL) and the mixture was allowed to warm to rt overnight. The solvent was removed under vacuum and the crude residue was purified by column chromatography to yield the title compound as a pale yellow crystalline solid (90%): HPLC (OD, 20% 2-propanol/hexanes = 20:80, 1.0 mL/min) T_r (*R*) (major) = 17.00 min, T_r (*S*) (minor) = 47.04 min, >99% ee; mp 88°; $[\alpha]_D$ + 102.4 (*c* 0.9467, $CHCl_3$); IR (film) 3193, 1774, 1719, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.37 (s, 0.85H), 9.10 (s, 0.15H), 8.01 (m, 2H), 7.85 (m, 2H), 7.42 (m, 2H), 7.38 (2H), 6.85 (s, 1H), 6.29 (s, 1H), 4.93 (m, 1H), 4.24 (m, 2H), 3.93, (m, 2.6H), 3.73 (s, 0.4H); ^{13}C NMR ($CDCl_3$) δ 172.5, 169.4, 168.2, 152.5, 148.5, 139.8, 134.8, 134.4, 131.4, 129.2, 128.7, 128.0, 123.9, 123.4, 122.9, 120.2, 64.4, 63.5, 54.5; HRMS–ESI$^+$ (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{17}Cl_2N_3NaO_8$, 580.0290; found 580.0282.

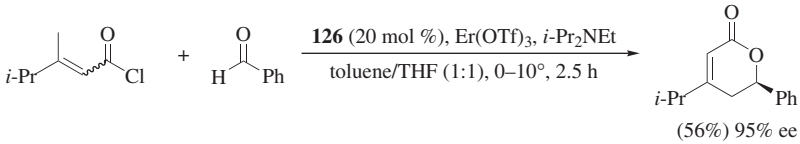


(76%) dr 95:5, 98% ee

(4*S*,5*R*)-2-(Ethylthio)-5-methyl-4-(2-phenylethyl)-4,5-dihydro-1,3-thiazin-6-one [*Cinchona* Alkaloid-Catalyzed [4 + 2] Ketene Thiocarbonyl Imine Cycloaddition].[139] To a solution of *O*-trimethylsilylquinine (**26**) (80 mg, 0.2 mmol) and ethyl (3-phenyl-1-tosylpropyl)carbamodithioate (394 mg, 1 mmol) in CH_2Cl_2 (9 mL) at $-78°$ was added *N*,*N*-diisopropylethylamine (0.61 mL, 3.5 mmol, 3.5 equiv). A solution of $LiClO_4$ (106 mg, 1.0 mmol, 1.0 equiv) in Et_2O (1.0 mL) was added and the mixture was stirred for 10 min. A solution of propionyl chloride (175 μL, 2.0 equiv, 2.0 mmol) in CH_2Cl_2 (0.5 mL) was added via syringe pump over 2 h. Once addition was complete, the mixture was stirred for 10 h at $-78°$. The reaction mixture was diluted with Et_2O (20 mL) and the resulting mixture was filtered through a silica gel pad (8 × 4 cm), eluting with additional Et_2O. The solvents were evaporated and the resulting crude product mixture was purified by chromatography on silica gel (EtOAc/hexanes = 2:98) to yield the title compound (222 mg, 76%) as a yellow oil: chiral stationary phase HPLC (Daicel Chiralpak OD-H column, 1.0 ml/min, 2-propanol/hexane = 2:98) T_r (4*R*,5*S*) = 9.4 min, T_r (4*S*,5*R*) = 14.6 min, (4*S*,5*R*)/(4*R*,5*S*) > 100:1, >98% ee; $[\alpha]_D + 0.5$ (*c* 2.12, $CHCl_3$); IR (film) 2976, 2928, 1707, 1593, 1454, 1142, 921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2H), 7.27–7.22 (m, 3H), 3.77 (dt, $J = 10.8$, 3.3 Hz, 1H), 3.27–3.11 (m, 1H), 3.06–2.97 (m, 1H), 2.85–2.75 (m, 1H), 2.68 (dq, $J = 7.2$, 3.3 Hz, 1H), 2.68–2.13 (m, 1H), 1.89–1.78 (m, 1H), 1.43 (t, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 154.9, 141.4, 128.4 (4C), 126.0, 65.8, 45.8, 33.3, 32.5, 25.7, 14.3, 9.6; HRMS (*m*/*z*): calcd for $C_{15}H_{19}NOS_2$, 293.0908; found 293.0900.



Ethyl (3*R*,4*R*)-3,4-Dihydro-3-ethyl-2-oxo-3,6-diphenyl-2*H*-pyran-4-carboxylate [Heterocyclic Carbene-Catalyzed Ketene [4 + 2] Cycloaddition with an Enone].[141] A mixture of triazolium salt **100** (60 mg, 0.1 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) in THF (2 mL) was stirred at rt for 10 min. The resulting solution was cooled to 0°, and the enone ethyl (*E*)-4-oxo-4-phenylbut-2-enoate (204.2 mg, 1.0 mmol) was added in one portion, followed by slow addition of a solution of ethylphenylketene (0.23 mL, 1.5 mmol) in THF (2.5 mL) via syringe pump over 1 h. After the full conversion of enone, the reaction mixture was allowed to warm to rt and stirred for 24 h. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography to give the title compound, which was recrystallized from *n*-hexane/2-propanol (9:1) to give the nearly pure *trans*-isomer as a colorless solid (79%): HPLC (Daicel Chiralpak AD-H column, 20°; 1.0 ml/min; 2-propanol/hexanes = 10:90) T_r (minor) = 10.0 min, T_r (major) = 13.6 min, 91% ee (98% ee after recrystallization); mp 106–108°; $[\alpha]_D^{25}$ − 266 (*c* 1.63, $CHCl_3$); IR (KBr) 2976, 1768, 1730, 1496, 1447, 1334, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 2H), 7.20–7.00 (m, 8H), 5.69 (d, $J = 7.0$ Hz, 1H), 4.09 (q, $J = 7.0$ Hz, 2H), 3.89 (d, $J = 7.0$ Hz, 1H), 2.22–2.10 (m, 1H), 1.90–1.80 (m, 1H), 1.14 (t, $J = 7.0$ Hz, 3H), 0.59 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 151.7, 136.2, 131.5, 129.1, 128.4, 128.1, 127.5, 126.4, 124.5, 97.2, 61.5, 50.7, 45.1, 29.2, 13.8, 7.8; HRMS–EI (*m*/*z*): calcd for $C_{22}H_{22}O_4$, 350.1518; found, 350.1523. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.22; H, 6.38.



(*R*)-4-Isopropyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one [Lewis Base Catalyzed Alkenyl Ketene [4 + 2] Cycloaddition].[144] A reaction flask was charged with activated $Er(OTf)_3$ (313 mg, 0.51 mmol). Tetrahydrofuran (0.9 mL), toluene (0.8 mL), and a solution of (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (**126**) (14 mg, 0.068 mmol) in THF (0.3 mL) were added to the flask and the mixture was stirred for 15 min at rt. After cooling to −10°, *N*,*N*-diisopropylethylamine (0.15 mL, 0.85 mmol) and benzaldehyde (35 μL, 0.34 mmol) were

successively added. A solution of 3,4-dimethylpent-2-enoyl chloride (49.8 mg, 0.34 mmol) in toluene (0.5 mL) was then added over 30 min using a syringe pump. After stirring for an additional 2 h at $-10°$, the reaction mixture was filtered through a plug of silica gel (2 cm, hexanes/EtOAc = 1:1). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 4:1, $R_f = 0.29$) to furnish the title compound as a white solid (41.2 mg, 56%): HPLC (Chiralcel OD-H column, 25 cm, 1 mL/min, $\lambda = 220$ nm, hexane/2-propanol = 95:5) 95% ee; mp 48.1−49.3°; $[\alpha]_D^{23.9} + 184$ (*c* 1.05, $CHCl_3$); IR (neat) 2970, 1703, 1635, 1243, 1006, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.34 (m, *Ph*, 5H), 5.90 (m, C*H*CO, 1H), 5.36 (dd, $J = 11.8$, 4.0 Hz, C*H*Ph, 1H), 2.65 (ddd, $J = 17.7$, 11.8, 2.2 Hz, CH_2, 1H), 2.49 (m, $CH(CH_3)_2$, 1H), 2.47 (dd, $J = 17.7$, 4.0 Hz, CH_2, 1H), 1.14 (d, $J = 6.8$ Hz, $CH(CH_3)_2$, 3H), 1.13 (d, $J = 6.8$ Hz, $CH(CH_3)_2$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 165.2, 138.7, 128.5, 128.4, 125.9, 113.8, 78.9, 34.7, 34.2, 20.4, 19.9; HRMS–EI (*m/z*): calcd for $C_{14}H_{16}O_2$, 216.1150; found, 216.1146. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.46; H, 7.46.

TABULAR SURVEY

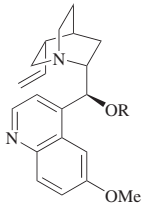
The tabular survey lists all catalytic asymmetric formal [2 + 2] or [4 + 2] cycloadditions reported from 1982, starting with the initial report by Wynberg, through 2010. The tables are organized according to experimental details of the ketene cycloaddition and the type of catalyst used for these reactions. Tables including closely related reaction types are divided into subtables organized according to ketene structure or method of ketene generation. For example, related ketene cycloadditions involving pregenerated ketene or in situ ketene generation appear in adjacent subtables. Table entries are listed by increasing number of carbon atoms in the ketene or ketene precursor, excluding commom protecting groups, simple alkyl or aryl groups on oxygen or nitrogen, and silyl groups. Entries for a given ketene, or ketene precursor, are then listed according to the number of carbon atoms in the cycloaddition partner also ignoring common protecting groups (e.g., trimethylsilyl, benzyl, *t*-butyl carbamoyl, etc.). Reaction yields for table entries are given in parentheses; (—) signifies that no yield or stereoselectivity data was available from the original report.

The following abbreviations (not included in *The Journal of Organic Chemistry* Standard Abbreviations and Acronymns) are used in the Tabular Survey:

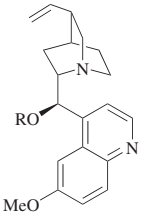
BTF	1,3-bis(trifluoromethyl)benzene
FVP	flash vacuum pyrolysis

KHMDS	potassium bis(trimethylsilyl)amide
MS	molecular sieves
Np	naphthyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl

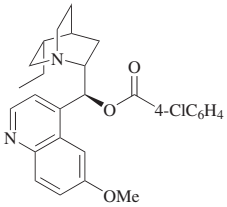
CHART 1. CATALYSTS AND CATALYST PRECURSORS USED IN TABLES



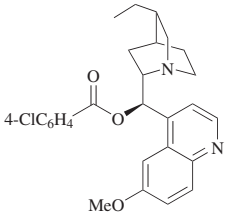
	R
1	H
1a	Ac
6	TMS
10	COEt



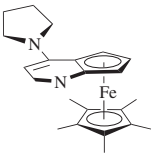
	R
2	H
5	TMS
5a	Me
9	Ac
11	COEt
12	Bz
13	TBS



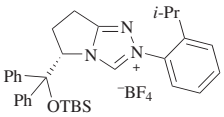
3



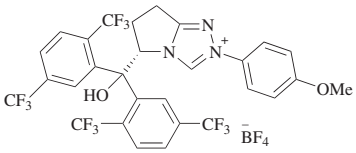
4



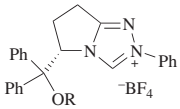
7



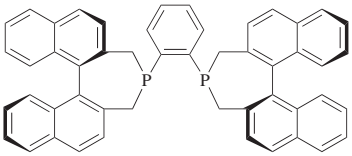
8



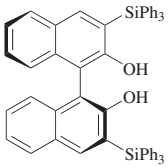
14



	R
15	TBS
15a	TMS

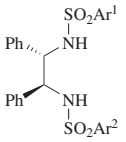


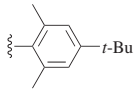
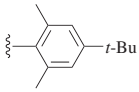
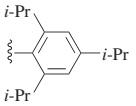
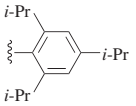
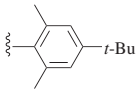
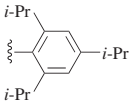
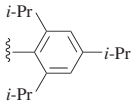
16

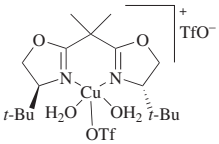


17

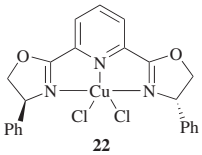
CHART 1. CATALYSTS AND CATALYST PRECURSORS USED IN TABLES (*Continued*)



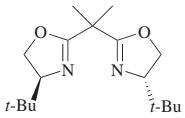
	Ar^1	Ar^2
18	4-MeC_6H_4	4-MeC_6H_4
19	C_6F_5	C_6F_5
20	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$
28	Mes	Mes
29		
30		Mes
31		
31a		



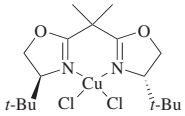
21



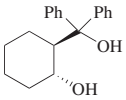
22



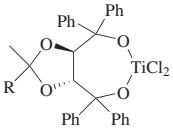
23



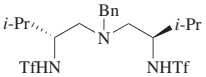
24



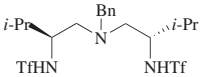
25



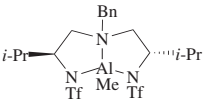
R	
26	Ph
27	Me



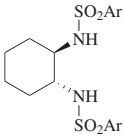
32

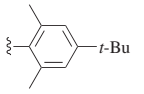
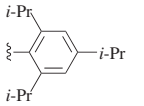


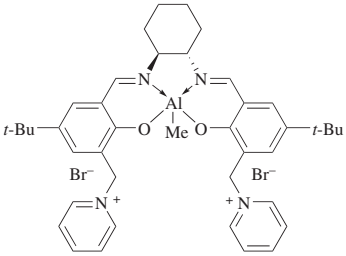
33



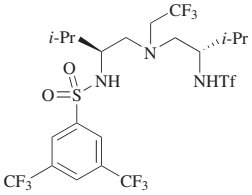
35



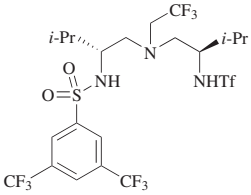
Ar	
34	
36	



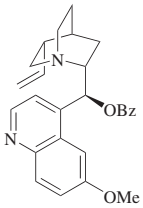
37



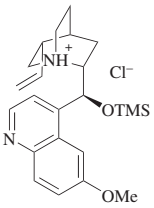
38



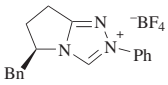
39



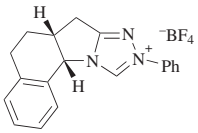
40



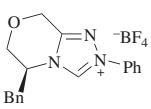
41



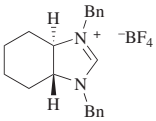
42



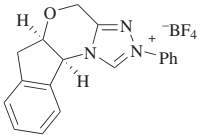
43



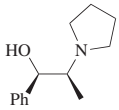
44



45



46



47

TABLE 1. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO ACTIVATED CARBONYL COMPOUNDS

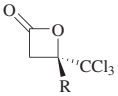
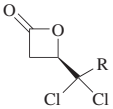
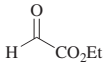
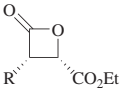
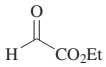
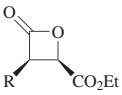
Ketene Source	Aldehyde or Ketone	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2				
		1 (2 mol %), toluene, –25° or –50°		63, 64
			R / (%) / % ee: CCl_3 (89) 98; $CHCl_2$ (67) 45; CCl_2Me (95) 91; CCl_2Et (87) 89; CCl_2n-Bu (90–95) 92; CCl_2Ph (89) 90; CCl_2n-C_6H_{13} (90–95) 92	64; 64; 64; 64; 65; 64; 65
		2 (2 mol %), toluene, –25° or –50°		64
			R / (%) / % ee: CCl_3 (89) 76; CCl_2Me (95) 76; CCl_2Et (87) 70; CCl_2Ph (89) 68	
		1 (2 mol %), toluene, –25°		64
			R / (%) / % ee: Me (72) 94; Et (1–2) —; 4-ClC_6H_4 (68) 90; 4-$O_2NC_6H_4$ (95) 89	
		2 (2 mol %), toluene, –25°		64
			R / (%) / % ee: Me (72) 85; 4-ClC_6H_4 (68) 65; 4-$O_2NC_6H_4$ (95) 65	
		1 (2 mol %), $(i\text{-Pr})_2NEt$, toluene, –25° to rt		67
			R / (%) / % ee: *i*-Pr (40) 98; *n*-C_6H_{13} (73) 93; $PivOCH_2CH_2$ (80) 94; Bn (85) 94	
C_{3-10}				
		**3** (10 mol %), Et_3N (10 mol %), $(i\text{-Pr})_2NEt$, $CHCl_3$, –60°		68
			R / (%) / dr / % ee: Me (55) >95:5 >95; Et (50) >95:5 >95; $TBDPSOCH_2CH_2$ (47) >95:5 >95; *i*-Pr (59) >95:5 >95; Bn (48) >95:5 >95; $PhCH_2CH_2$ (54) >95:5 >95	
C_{4-5}				
		**4** (10 mol %), Et_3N (10 mol %), $(i\text{-Pr})_2NEt$, $CHCl_3$, –60°		68
			R / (%) / dr / % ee: Et (58) >95:5 >95; *i*-Pr (60) >95:5 >95	

TABLE 2A. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO UNACTIVATED ALDEHYDES

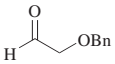
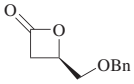
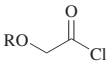
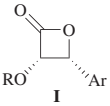
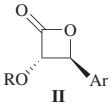
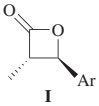
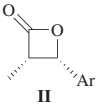
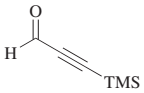
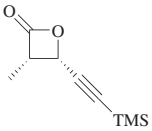
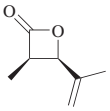
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_2		**5** (10 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 (70) 84% ee	72
		6 (10 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°		72
			R / % ee *t*-Bu (71) 96 *c*-C_6H_{11} (85) 94 $PhCH_2CH_2$ (80) 92	
		**6** (20 mol%), $Er(OTf)_3$ (15 mol %), $i\text{-Pr}_2NEt$, CH_2Cl_2, 0°	 + 	73
			I **II**	
			R / Ar / **I + II** / **I/II** / % ee **I** Ph / Ph / (58) / 88:12 / >99 Ph / 4-BrC_6H_4 / (55) / 88:12 / >99 Ph / 3-ClC_6H_4 / (88) / 92:8 / >99 Bn / 4-NCC_6H_4 / (68) / 87:13 / >99	
C_3		**6** (15 mol%), $Sc(OTf)_3$ (15 mol %), $i\text{-Pr}_2NEt$, CH_2Cl_2/Et_2O, 0°	 + 	73
			I **II**	
			Ar / **I + II** / **I/II** / % ee **I** Ph / (75) / 91:9 / 92 4-$O_2NC_6H_4$ / (82) / 91:9 / 96 4-NCC_6H_4 / (80) / 92:8 / 99	
		6 (10 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°	+	
			I **II**	
			R / **I + II** / **I/II** / % ee **I** Et / (74) / 99:1 / 98	146
			c-C_6H_{11} / (74) / >98:2 / 97	72
			2-ClC_6H_4 / (80) / 98:2 / 99	72
			$PMBOCH_2CH_2$ / (70) / 89:11 / 99	75
		**6** (10 mol %), $MgCl_2$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (3:1), –78°	 (92) 98% ee	147
		5 (10 mol %), LiI, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –40°	 (62) 98% ee	146

TABLE 2A. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO UNACTIVATED ALDEHYDES (*Continued*)

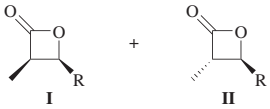
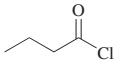
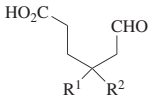
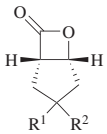
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
		5 (10 mol %), $LiClO_4$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 **I** + **II**	72
			R / **I + II** / **I/II** / % ee **I**: *i*-Bu (72) 95:5 99; Ph (78) 98:2 >99; 4-FC_6H_4 (85) >98:2 >99; 2-MeC_6H_4 (76) >98:2 >99; $PhCH_2CH_2$ (84) 98:2 >99; $BnOCH_2$ (68) 88:12 99; $CH_2{=}CH(CH_2)_8$ (74) 95:5 99	
C_4 		**6** (15 mol%), $Sc(OTf)_3$ (15 mol %), $i\text{-}Pr_2NEt$, CH_2Cl_2/Et_2O, 0°	**I** (80), **I/II** 95:5, 99% ee **I**	73
C_{6-8} 	Intramolecular	**1a** (10 mol %), Me (3 eq), $(i\text{-}Pr)_2NEt$, MeCN, rt	 R^1 / R^2 / % ee: H, H (54) 92; —OCH_2CH_2O— (37) 92; Me, Me (45) 90	81

TABLE 2B. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO ENANTIOENRICHED ALDEHYDES

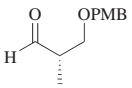
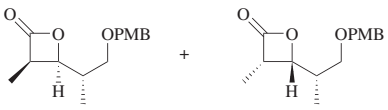
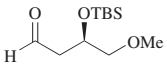
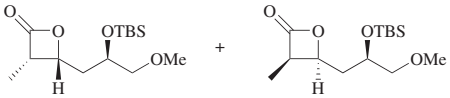
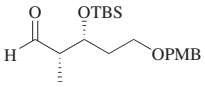
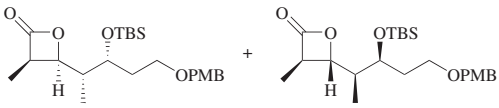
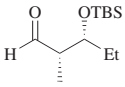
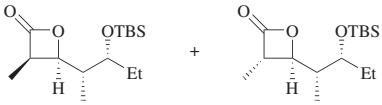
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_3		**5** (10 mol %), $LiClO_4$, $(i\text{-}Pr_2)NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (74), **I/II** = 92:8 **II**	75
		**6** (10 mol %), $LiClO_4$, $(i\text{-}Pr_2)NEt$, CH_2Cl_2/Et_2O (4:1), –78°	 **I** **I** (74), **I/II** > 97:3 **II**	147
		**5** (10 mol %), LiI, $(i\text{-}Pr_2)NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (91), **I/II** > 98:2 **II**	75
		**5** (10 mol %), LiI, $(i\text{-}Pr_2)NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (95), **I/II** > 95:5 **II**	146

TABLE 2B. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO ENANTIOENRICHED ALDEHYDES (*Continued*)

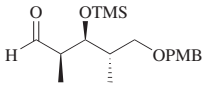
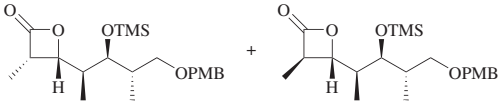
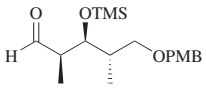
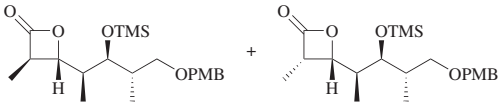
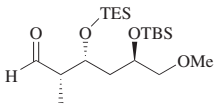
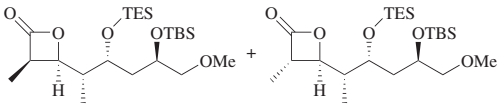
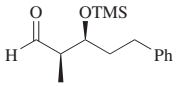
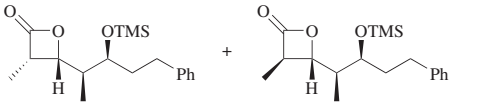
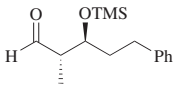
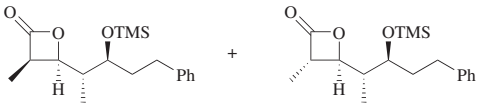
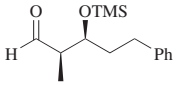
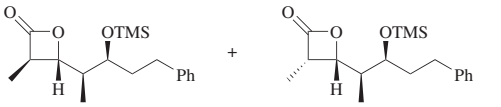
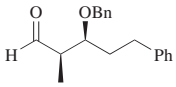
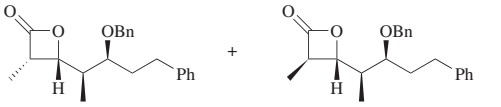
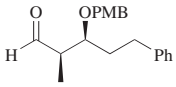
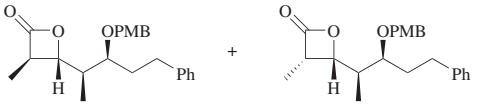
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_3				
		**6** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –40°	 **I** **I** (84), **I/II** = 97:3 **II**	75
		**5a** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –40°	 **I** **I** (72), **I/II** = 96:4 **II**	75
		**5** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (77), **I/II** > 97:3 **II**	147
		**6** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/DMF (11:1), –50°	 **I** **I** (83), **I/II** > 98:2 **II**	75
		**5** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/THE (10:1), –78°	 **I** **I** (81), **I/II** > 98:2 **II**	75
		**5a** (10 mol %), $LiClO_4$, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (81), **I/II** = 96:4 **II**	75
		**6** (10 mol %), $LiClO_4$, (i-Pr_2)NEt, CH_2Cl_2/THF (9:1), –40°	 **I** **I** (76), **I/II** > 98:2 **II**	75
		**5** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –78°	 **I** **I** (81), **I/II** = 96:4 **II**	75

TABLE 2B. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO ENANTIOENRICHED ALDEHYDES (*Continued*)

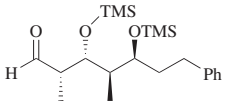
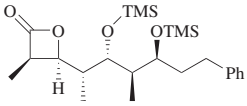
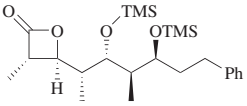
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_3				
		**5** (10 mol %), LiI, (i-Pr_2)NEt, CH_2Cl_2/Et_2O (9:1), –78°	 +  **I** **I** (79), **I/II** > 98:2 **II**	75

TABLE 3. Fe(II)–AZAINDENE-CATALYZED CYCLOADDITIONS TO ALDEHYDES

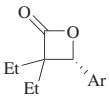
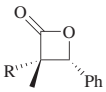
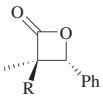
Ketene	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_4				
		7 (5 mol %), THF, –78°	(76) 68% ee	79
C_6				
		7 (5 mol %), THF, –78°		79
			Ar — % ee Ph (92) 91 4-MeC_6H_4 (67) 89 4-$CF_3C_6H_4$ (74) 80 4-$AcOC_6H_4$ (76) 81 2-Np (77) 89	
C_{6-8}				
		7 (5 mol %), THF, –78°	 +  **I** **II**	79
			R — **I + II** — **I/II** — % ee **I** *i*-Pr (48) 4.1:1 91 *c*-C_5H_9 (53) 4.5:1 88	

TABLE 3. Fe(II)-AZAINDENE-CATALYZED CYCLOADDITIONS TO ALDEHYDES (*Continued*)

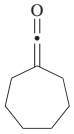
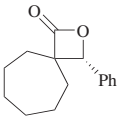
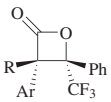
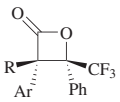
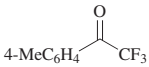
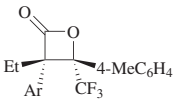
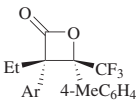
Ketene	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_8				
		**7** (5 mol %), THF, –78°	 (71) 82% ee	79

TABLE 4. TRIAZOLIUM CARBENE-CATALYZED CYCLOADDITIONS TO TRIFLUOROMETHYL KETONES

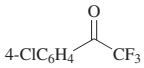
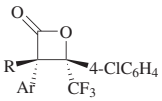
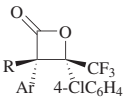
Ketene	Ketone	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
$C_{9–11}$				
		8 (12 mol %), Cs_2CO_3 (10 mol %), toluene, –40°	 **I** +  **II**	80

Ar	R	**I + II**	**I/II**	% ee **I**
Ph	Me	(76)	23:1	99
Ph	Et	(81)	6:1	97
4-ClC_6H_4	Et	(50)	14:1	—
4-MeC_6H_4	Et	(86)	7:1	95
4-$MeOC_6H_4$	Et	(90)	7:1	93

Ketene	Ketone	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
$C_{10–11}$				
		**8** (12 mol %), Cs_2CO_3 (10 mol %), toluene, –40°	 **I** +  **II**	80

Ar	**I + II**	**I/II**	% ee **I**
Ph	(56)	7:1	96
4-MeC_6H_4	(60)	7:1	—

TABLE 4. TRIAZOLIUM CARBENE-CATALYZED CYCLOADDITIONS TO TRIFLUOROMETHYL KETONES (*Continued*)

Ketene	Ketone	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_{10-12}				
		**8** (12 mol %), Cs_2CO_3 (10 mol %), toluene, –40°	 **I** +  **II**	80

Ar	R	**I + II**	**I/II**	% ee **I**
Ph	Et	(89)	9:1	98
4-ClC_6H_4	Et	(90)	16:1	93
4-BrC_6H_4	Et	(83)	16:1	93
4-MeC_6H_4	Me	(96)	12:1	99
4-MeC_6H_4	Et	(93)	11:1	99
4-$MeOC_6H_4$	Et	(95)	11:1	97
Ph	*n*-Pr	(99)	4:1	—
Ph	*n*-Bu	(81)	6:1	—

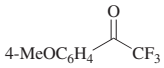
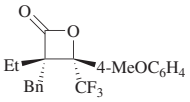
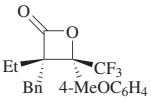
C_{11}				
		**8** (12 mol %), Cs_2CO_3 (10 mol %), toluene, –40°	 **I** +  **II** **I + II** (99), **I/II** = 50:50 91% ee **I**	80

TABLE 5A. *CINCHONA* ALKALOID-CATALYZED DIMERIZATION OF MONOSUBSTITUTED KETENES

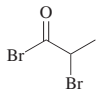
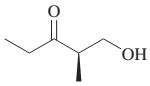
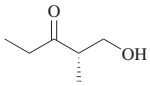
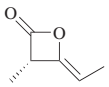
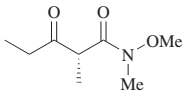
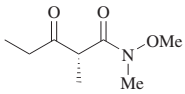
Ketene Source	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*			
C_3			
	1. Zn, THF, –78° 2. Catalyst (1 mol %), –78° 3. $LiAlH_4$, THF, –78°	 Catalyst (%) % ee **1** (20) 98 **6** (20) 98 **10** (20) 97	84
	1. Zn, THF, –78° 2. Catalyst (1 mol %), –78° 3. $LiAlH_4$, THF, –78°	 Catalyst (%) % ee **2** (20) 70 **5** (20) 93 **11** (20) 54	84
	6 (5 mol%), $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt	 (66) —% ee	151
	1. Catalyst (5 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt 2. MeO(Me)NH, 2-pyridone (10 mol %), CH_2Cl_2, rt	 Catalyst (%) % ee **2** (56) 70 **5** (79) 94 **11** (65) 69 **12** (64) 80 **13** (72) 94	87
	1. **5** (5 mol %), $(i\text{-Pr})_2NEt$, toluene, rt 2. MeO(Me)NH, 2-pyridone (10 mol %), CH_2Cl_2, rt	 (19) 93% ee	87

TABLE 5A. *CINCHONA* ALKALOID-CATALYZED DIMERIZATION OF MONOSUBSTITUTED KETENES (*Continued*)

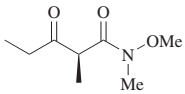
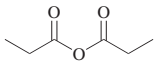
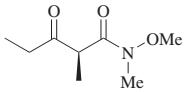
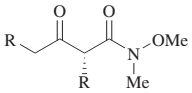
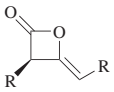
Ketene Source	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*			
C_3	1. **6** (5 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt 2. MeO(Me)NH, 2-pyridone (10 mol %), CH_2Cl_2, rt	 (79) 97% ee	87
	1. FVP, 500–550° 2. **1** (0.3 mol %), THF, –78° 3. LiN(Me)OMe, THF, –78°	 (65) 99% ee	148
C_{3-6}	1. **5** (5 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt 2. MeO(Me)NH, pyridone (10 mol %), CH_2Cl_2, rt	 R / % ee $TIPSOCH_2$ (88) 91 Et (82) 92 MeO_2CCH_2 (64) 92 *i*-Pr (65) 96 *t*-Bu (58) 92	87
C_{4-12}	**5** (5 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt	 R / % ee MeO_2CCH_2 (60) 92 *n*-Bu (75) 96 *c*-$C_5H_9CH_2$ (54) 94 *c*-$C_6H_{11}CH_2$ (55) 90 $PhCH_2$ (48) 96 $MeO(CH_2)_{10}$ (62) —	88

TABLE 5B. LEWIS BASE CATALYZED DIMERIZATION OF DISUBSTITUTED KETENES

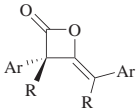
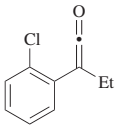
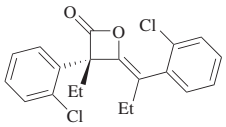
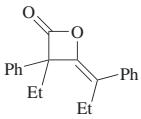
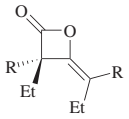
Ketene	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*			
C_{9-12}	**14** (10 mol %), Cs_2CO_3 (10 mol %), THF, rt	 Ar / R / % ee Ph Me (72) 84 Ph *n*-Pr (56) 92 4-ClC_6H_4 *n*-Bu (71) 97	89
C_{10} 	**15** (10 mol %), Cs_2CO_3 (10 mol %), THF, rt	 (46) 28% ee	89
	16 (10 mol %), CH_2Cl_2, –78°	 (65) 80% ee[a]	90

TABLE 5B. LEWIS BASE CATALYZED DIMERIZATION OF DISUBSTITUTED KETENES (*Continued*)

Ketene	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*			
C_{10-11}			
	14 (10 mol %), Cs_2CO_3 (10 mol %), THF, rt		89

R		% ee
Ph	(83)	96
2-ClC_6H_4	(trace)	—
3-ClC_6H_4	(70)	96
4-ClC_6H_4	(99)	94
4-BrC_6H_4	(83)	94
4-MeC_6H_4	(63)	95
4-$MeOC_6H_4$	(61)	89

[a] The configuration of the product was not determined.

TABLE 6A. LEWIS ACID CATALYZED CYCLOADDITIONS OF PREGENERATED KETENES TO ALDEHYDES

Ketene	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2				
		17 (1 eq), $AlMe_3$ (1 eq), toluene, –78°		96

R		% ee
Me	(78)	23
Et	(33)	45
n-Pr	(69)	45
i-Pr	(59)	28
n-Bu	(80)	17
Ph	(76)	21

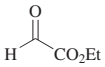
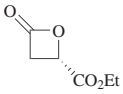
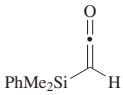
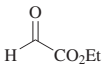
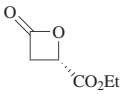
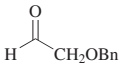
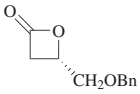
		Ligand (10 mol %), $AlMe_3$ (10 mol %), toluene, –78°		97

Ligand		% ee
18	(13)	0
19	(94)	10

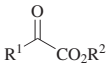
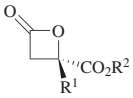
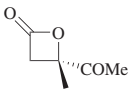
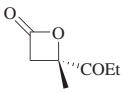
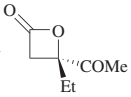
		20 (10 mol %), $Al(R^2)_3$ (10 mol %), toluene, –78°		97

R^1	R^2		% ee
Et	Me	(55)	20
Et	*i*-Bu	(72)	23
Et	Et	(77)	33
Me	Et	(59)	30
i-Pr	Et	(76)	56
t-Bu	Et	(77)	65
n-Bu	Et	(82)	41
c-C_6H_{11}	Et	(75)	74
Ph	Et	(11)	14

TABLE 6B. LEWIS ACID CATALYZED CYCLOADDITIONS OF TRIALKYLSILYLKETENES TO CARBONYL COMPOUNDS

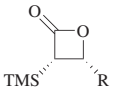
Ketene	Carbonyl Compound	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_2				
		1. **21** (1 mol %), 3 Å MS, THF, –78° 2. KF, MeCN	 (77) 93% ee	104
		1. **23** (25 mol %), $Cu(OTf)_2$ (20 mol %), THF, –78° 2. KF, MeCN	 (99) 92% ee	104
		1. **22** (20 mol %), $AgSbF_6$ (44 mol %), CH_2Cl_2, –40° 2. KF, MeCN	 (92) 87% ee	104
		1. **27** (20 mol %), CH_2Cl_2, –15° 2. KF•$2H_2O$, MeCN		102

R		% ee
$BnO(CH_2)_4$	(76)	28
n-Bu	(49)	41
c-C_6H_{11}	(66)	80
4-$O_2NC_6H_4$	(71)	21
Bn	(58)	9
$PhCH_2CH_2$	(78)	34

	1. **25** (20 mol %), toluene, –78 to –26° 2. KF•$2H_2O$, MeCN		101
	1. **24** (10 mol %), $AgSbF_6$ (22 mol %), CH_2Cl_2, –50° 2. KF, MeCN		104
	1. **24** (10 mol %), $AgSbF_6$ (22 mol %), CH_2Cl_2, –50° 2. KF, MeCN	 (82) 98% ee	104
	1. **24** (10 mol %), $AgSbF_6$ (22 mol %), CH_2Cl_2, –50° 2. KF•$2H_2O$, MeCN	 (83) 84% ee +  (4)	104

R^1	R^2		% ee
Me	Me	(93)	95
Et	Me	(89)	93
$BrCH_2$	Et	(75)	91
i-Bu	Me	(89)	86
i-Pr	Et	(78)	88
Ph	Me	(76)	83

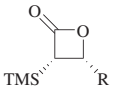
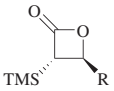
TABLE 6B. LEWIS ACID CATALYZED CYCLOADDITIONS OF TRIALKYLSILYLKETENES TO CARBONYL COMPOUNDS (*Continued*)

Ketene	Carbonyl Compound	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2		**25** (20 mol %), Et_2AlCl (17 mol %), toluene, –78 to –26°		101

R		dr	% ee
n-C_4H_9	(86)	>99:1	85
c-C_6H_{11}	(83)	>99:1	84
Ph	(82)	>99:1	28

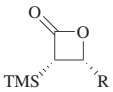
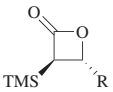
		1. **26** (20 mol %), CH_2Cl_2, –15° 2. $KF{\bullet}2H_2O$, MeCN		102

R		% ee
$BnOCH_2$	(39)	0
$BnO(CH_2)_2$	(79)	20
$BnO(CH_2)_3$	(53)	35
$BnO(CH_2)_4$	(66)	43
$PhCH_2CH_2$	(78)	27

		28 (x eq), $AlMe_3$ (x eq), toluene, –80 to –30°	 + 	100

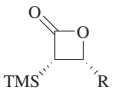
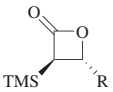
I **II**

R	x	**I**	**I/II**	% ee **I**
c-C_6H_{11}	0.98	(57)	95:5	55
Bn	0.44	(43)	100:0	40
$PhCH_2CH_2$	0.61	(43)	100:0	44

		29 (x eq), $AlMe_3$ (x eq), toluene, –80 to –30°	 + 	100

I **II**

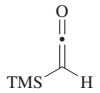
R	x	**I + II**	**I/II**	% ee **I**
c-C_6H_{11}	0.33	(32)	85:15	68
Bn	0.50	(56)	83:17	83
$PhCH_2CH_2$	0.30	(80)	90:10	44
4-$MeOC_6H_4CH_2$	0.30	(77)	99:1	83
n-$C_{11}H_{23}$	0.29	(67)	94:6	47

		30 (x eq), $AlMe_3$ (x eq), toluene, –80 to –30°	 + 	100

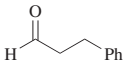
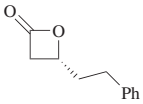
I **II**

R	x	**I + II**	**I/II**	% ee **I**
c-C_6H_{11}	0.51	(57)	77:23	53
Bn	0.29	(82)	79:21	62
$PhCH_2CH_2$	0.25	(85)	90:10	30

TABLE 6B. LEWIS ACID CATALYZED CYCLOADDITIONS OF TRIALKYLSILYLKETENES TO CARBONYL COMPOUNDS (*Continued*)

Ketene	Carbonyl Compound	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_2				
		**31** (*x* eq), toluene, –80 to –30°	**I** + **II**	100

R	*x*	**I + II**	**I/II**	% ee **I**
c-C_6H_{11}	0.33	(43)	69:31	67
Bn	0.30	(72)	75:25	82
$PhCH_2CH_2$	0.29	(82)	94:6	36
PMB	0.29	(81)	70:30	75
n-$C_{11}H_{23}$	0.30	(67)	82:18	48

		1. **27** (20 mol %), CH_2Cl_2, –15° 2. KF•$2H_2O$, MeCN		102

R		% ee
TES	(74)	26
TBS	(75)	31
$PhMe_2Si$	(75)	26

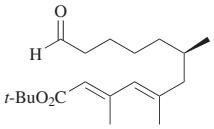
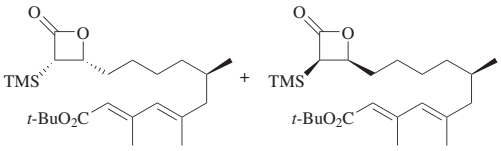
		**29** (52 mol %), $AlMe_3$ (50 mol %), toluene, –70 to 0°	 **I** **I + II** (75), **I/II** = 75:25 (**I** *cis/trans* = 94:6) **II**	99

TABLE 7. Al(III)-CATALYZED CYCLOADDITIONS OF IN SITU GENERATED KETENES TO ALDEHYDES

Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_2				
		32 (10 mol %), $AlMe_3$ (10 mol %), $(n\text{-Bu})_4NBr$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78°	(92) >99% ee	153

		33 (10 mol %), Me_2AlCl (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –78°		105

R	Temp (°)		% ee
$TBDPSOCH_2$	−40	(74)	89
c-C_6H_{11}	−40	(56)	54
$BnOCH_2$	−40	(91)	92
$BnOCH_2CH_2$	−40	(90)	91
$CH_2{=}CH(CH_2)_8$	−50	(91)	91

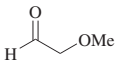
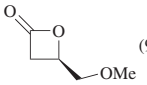
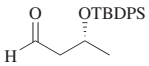
		**33** (10 mol %), Me_2AlCl (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –60°	 (91) 95% ee	147
		**32** (10 mol %), $AlMe_3$ (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –50°	**I** **I** (86), **I/II** = 97:3 **II**	153

TABLE 7. Al(III)-CATALYZED CYCLOADDITIONS OF IN SITU GENERATED KETENES TO ALDEHYDES (*Continued*)

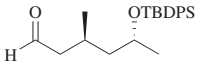
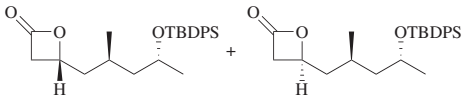
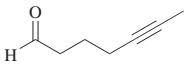
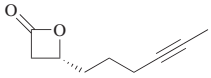
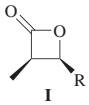
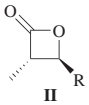
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2				
		29 (10 mol %), $AlEt_3$ (15 mol %), $(i\text{-Pr})_2NEt$, toluene, –85°	R % ee *t*-Bu (83) 78 Et_2CH (94) 80 *c*-C_5H_9 (90) 80 *c*-C_6H_{11} (88) 90	114
		34 (10 mol %), $AlEt_3$ (15 mol %), $(i\text{-Pr})_2NEt$, toluene, –85°	R % ee *t*-Bu (89) 75 Et_2CH (87) 68 *c*-C_5H_9 (81) 80 *c*-C_6H_{11} (87) 86	114
		35 (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2	R Temp (°) % ee *i*-Bu –50 (80) 93 *t*-BuC≡C –50 (91) 85 $PhCH_2CH_2$ –50 (93) 92 $PhCH_2CH_2$ –78 (89) 95 $BnOCH_2C{\equiv}C$ –50 (74) 89	105
		36 (10 mol %), $(i\text{-Bu})_2AlH$ (15 mol %), $(i\text{-Pr})_2NEt$, toluene, –85°	R % ee $MeC(=CH_2)CH_2CH_2$ (92) 88 *i*-Bu (84) 84 $TMSCH_2CH_2$ (82) 84 *n*-C_7H_{15} (86) 84	114
		29 (10 mol %), $(i\text{-Bu})_2AlH$ (15 mol %), $i\text{-Pr}_2NEt$, toluene, –85°	R % ee $MeC(=CH_2)CH_2CH_2$ (34) 74 $TMSCH_2CH_2$ (71) 79 $PhCH_2CH_2$ (66) 82	114
		**32** (15 mol %), $AlMe_3$ (15 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –50°	 **I** **I** (90), **I/II** = 92:8 **II**	153
		**32** (10 mol %), Me_2AlCl (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –60°	 (75) 95% ee	147
		31a (10 mol %), $(i\text{-Bu})_2AlH$ (15 mol %), $(i\text{-Pr})_2NEt$, toluene, –85°	(44) 73% ee R % ee *i*-Bu (98) 85 *n*-C_7H_{15} (44) 73	114

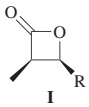
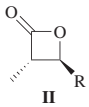
TABLE 7. Al(III)-CATALYZED CYCLOADDITIONS OF IN SITU GENERATED KETENES TO ALDEHYDES (*Continued*)

Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_3				
		35 (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –50°	 **I** +  **II**	108

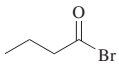
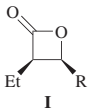
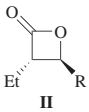
R	I + II	I/II	% ee I
$BnOCH_2$	(78)	88:12	94
$BnOCH_2C{\equiv}C$	(85)	91:9	94
$PMBOCH_2CH_2C{\equiv}C$	(86)	87:13	90
$TMSC{\equiv}C$	(90)	>99:1	93
$t\text{-}BuC{\equiv}C$	(90)	>99:1	90
$4\text{-}O_2NC_6H_4$	(90)	>99:1	98
$n\text{-}C_5H_{11}C{\equiv}C$	(85)	98:2	>93
$PhC{\equiv}C$	(83)	>99:1	91

		37 (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –70°	**I** + **II**	116

R	I + II	I/II	% ee I
Et	(76)	95:5	87
n-Pr	(67)	97:3	93
n-Bu	(64)	97:3	89
i-Bu	(76)	94:6	87
$CH_2{=}CH(CH_2)_3$	(74)	96:4	88
$n\text{-}C_7H_{15}$	(77)	96:4	87
$PhCH_2CH_2$	(82)	97:3	88

		38 (*x* mol %), $AlMe_3$ (*x* mol %), $(i\text{-Pr})_2NEt$, $C_6H_5CF_3$, –25°	 **I** +  **II**	112

R	*x*	I + II	I/II	% ee I
$BnOCH_2CH_2$	20	(75)	86:14	91
$TMSC{\equiv}C$	10	(76)	98:2	95
Ph	10	(80)	>98:2	96
$PhCH_2CH_2$	20	(71)	95:5	90
$CH_2{=}CH(CH_2)_8$	20	(77)	94:6	88

C_4				
		**38** (10 mol %), $AlMe_3$ (10 mol %), $(i\text{-Pr})_2NEt$, $C_6H_5CF_3$, –25°	 **I** +  **II**	112

R	I + II	I/II	% ee I
$BnOCH_2$	(78)	89:11	93
$BnOCH_2CH_2$	(83)	88:12	91
Ph	(83)	>98:2	94
$PhCH_2CH_2$	(81)	95:5	91

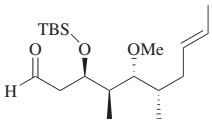
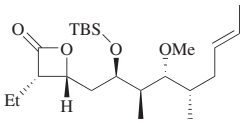
		**39** (50 mol %), $AlMe_3$ (50 mol %), $(i\text{-Pr})_2NEt$, BTF, –25°	 (65)	75

TABLE 7. Al(III)-CATALYZED CYCLOADDITIONS OF IN SITU GENERATED KETENES TO ALDEHYDES (*Continued*)

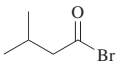
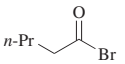
Ketene Source	Aldehyde	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_5				
		**38** (10 mol %), $(i\text{-Pr})_2NEt$, $C_6H_5CF_3$, –25°	 R / dr / % ee TMSC≡C (71) >98:2 94 Ph (84) >98:2 96	112
		**38** (10 mol %), $(i\text{-Pr})_2NEt$, $C_6H_5CF_3$, –25°	 **I** + **II** R / **I** / **I/II** / % ee **I** $BnOCH_2CH_2$ (88) 91:9 91 Ph (85) >98:2 96	112
		37 (10 mol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, –70°	 **I** + **II** R / **I + II** / **I/II** / % ee **I** Et (63) 97:3 94 *n*-Pr (93) 98:2 95 *n*-Bu (92) 96:4 93 *i*-Bu (76) 96:4 94 $CH_2{=}CH(CH_2)_3$ (96) 98:2 95 $PhCH_2CH_2$ (91) 98:2 94	116

TABLE 8A. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO IMINES

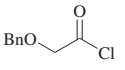
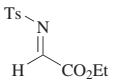
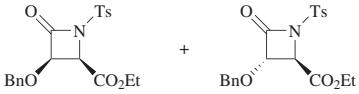
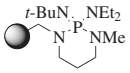
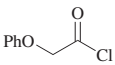
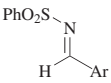
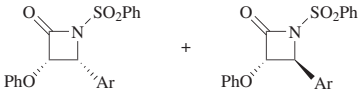
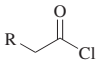
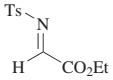
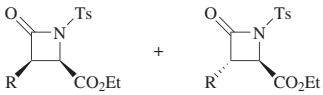
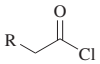
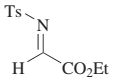
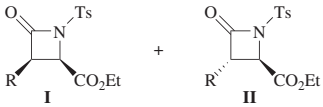
Ketene Source	Imine or Imine Precursor	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2				
		**12** (10 mol %), base, additive, toluene	 **I** + **II** Base / Additive / Temp (°) / **I + II** / **I/II** / % ee **I** K_2CO_3 / — / –78 to rt / (56) / 8:1 / 93	66
			 / — / –78 to rt / (60) / 99:1 / 99	66
			NaH / 15-crown-5 / –78 to rt / (60) / 25:1 / 99	66
			Proton Sponge / — / –78 / (57) / 99:1 / 99	66, 118
			Proton Sponge / $In(OTf)_3$ / –78 / (98) / 11:1 / 96	120
		**41** (15 mol %), $Sc[N(TMS)_2]_3$ (15 mol %), CH_2Cl_2, $(i\text{-Pr})_2NEt$, 0°	 **I** + **II** Ar / **I + II** / **I/II** / % ee **I** Ph (68) 18:1 92 $4\text{-}FC_6H_4$ (47) 19:1 97 $4\text{-}ClC_6H_4$ (57) 28:1 97 $4\text{-}BrC_6H_4$ (70) 14:1 97 $4\text{-}NCC_6H_4$ (52) 12:1 94 $4\text{-}MeC_6H_4$ (69) 19:1 95 $4\text{-}O_2NC_6H_4$ (55) 16:1 94 $4\text{-}CF_3C_6H_4$ (67) 18:1 95 $3,5\text{-}Cl_2C_6H_3$ (66) 14:1 96	125

TABLE 8A. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO IMINES (*Continued*)

Ketene Source	Imine or Imine Precursor	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_{2-9}				
		**12** (10 mol %), NaH, 15-crown-5, toluene, –78° to rt	 **I** + **II**	122
			R / **I + II** / **I/II** / % ee **I**: BnO (65) 25:1 99; Bn (60) 6:1 99	
		**12** (10 mol %), Proton Sponge, toluene, –78°	 **I** + **II**	
			R / **I + II** / **I/II** / % ee **I**: N_3 (47) 25:1 98	66
			Br (61) 98:2 96	66
			AcO (61) >99:1 98	66, 118
			PhO (45) 99:1 99	66, 118
			$PhOCH_2$ (53) 50:7 >95	66
			Et (57) 99:1 99	66, 118
			CH_2=CH (58) 99:1 98	66
			Ph (65) 99:1 99	66, 118
			Bn (60) 33:1 96	66

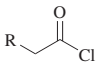
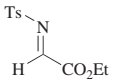
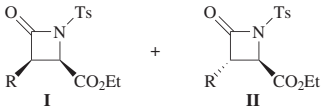
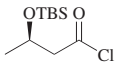
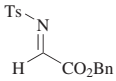
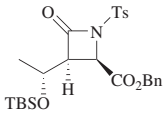
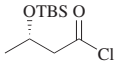
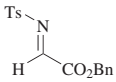
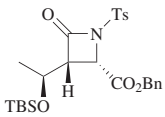
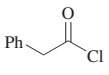
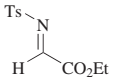
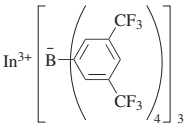
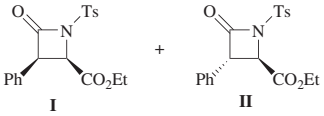
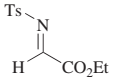
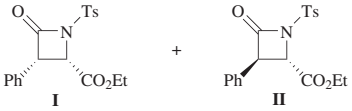
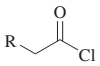
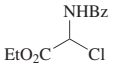
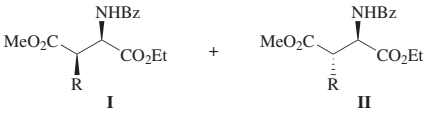
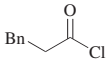
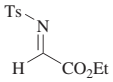
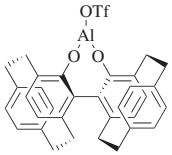
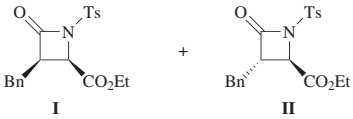
C_{2-9}				
		**12** (10 mol %), $In(OTf)_3$ (10 mol %), Proton Sponge, toluene, –78°	 **I** + **II**	120
			R / **I + II** / **I/II** / % ee **I**: Br (91) 10:1 96	
			PhO (93) 22:1 97	
			AcO (92) 34:1 98	
			$PhOCH_2$ (93) 12:1 96	
			CH_2=CH (92) 10:1 96	
			Ph (95) 60:1 98	
			Bn (94) 9:1 98	
C_4				
		**12** (10 mol %), $In(OTf)_3$ (10 mol %), Et_3N, toluene, –78°	 (59%) 99% ee	155
		**40** (10 mol %), $In(OTf)_3$ (10 mol %), Et_3N, toluene, –78°	 (53) 99% ee	155

TABLE 8A. *CINCHONA* ALKALOID-CATALYZED CYCLOADDITIONS TO IMINES (*Continued*)

Ketene Source	Imine or Imine Precursor	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_8				
		**12** (10 mol %),  (10 mol %), Proton Sponge, toluene, –78°	 **I** + **II** (80), **I/II** = 15:1, 95% ee **I**	120
		**40** (10 mol %), Proton Sponge, toluene, –78°	 **I** + **II** (64), **I/II** = 99:1, 99% ee **I**	66
C_{2-9}				
		1. **12** (10 mol %), Proton Sponge, toluene, –78° to rt 2. MeOH, reflux	 **I** **II**	123, 124
C_9				
		**12** (10 mol %),  (10 mol %), Proton Sponge, toluene, –78°	 **I** **II** **I** + **II** (85), **I/II** = 99:1, 99% ee **I**	121

R	I + II	I/II	% ee I
PhO	(63)	14:1	95
Ph	(62)	12:1	95
4-ClC_6H_4	(60)	12:1	94
4-$MeOC_6H_4$	(62)	10:1	94
4-$MeOC_6H_4O$	(53)	11:1	96

TABLE 8B. Fe(II)–4-AZAINDENE-CATALYZED CYCLOADDITIONS OF DISUBSTITUTED KETENES TO IMINES

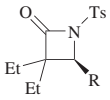
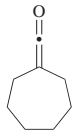
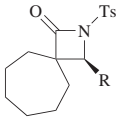
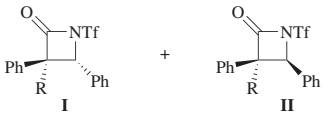
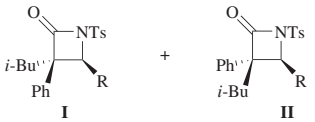
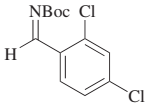
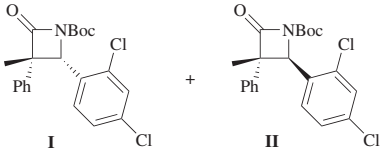
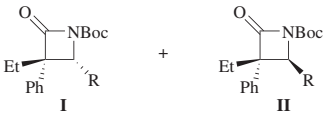
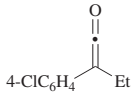
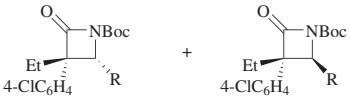
Ketene	Imine	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_6				
		7 (10 mol %), toluene, rt	 R: 2-C_4H_3O (93) % ee 92; (*E*)-PhCH=CH (83) % ee 92	126
C_8				
		**7** (10 mol %), toluene, rt	 R: *c*-C_3H_5 (89) % ee 94; 2-C_4H_3O (90) % ee 92; Ph (84) % ee 81; *c*-C_6H_{11} (76) % ee 94; (*E*)-PhCH=CH (82) % ee 91	126
C_9				
		7 (10 mol %), toluene or CH_2Cl_2, rt	**I** + **II**; R: Ph (83) **I + II**, 98:2 **I/II**, 81 % ee **I**; 4-FC_6H_4 (84), 96:4, 85; 2-BrC_6H_4 (79), 80:20, 84; 4-$CF_3C_6H_4$ (80), 97:3, 69; 4-$MeOC_6H_4$ (76), 81:19, 82; 2-MeC_6H_4 (89), 81:19, 99; 2-Np (76), 98:2, 94	127
C_{10}				
		7 (10 mol %), toluene, rt	**I** + **II**; R: 2-C_4H_3O (97) **I + II**, 9:1 **I/II**, 95 % ee **I**; *c*-C_3H_5 (98), 10:1, 98	126
$C_{10–12}$				
		7 (10 mol %), toluene, rt	 **I** + **II**; R: Et (60) **I + II**, 86:14 **I/II**, 63 % ee **I**; *i*-Bu (72), 97:3, 63	127
C_{12}				
		7 (10 mol %), toluene, rt	 **I** + **II**; R: *c*-C_3H_5 (88) **I + II**, 15:1 **I/II**, 89 % ee **I**; 2-C_4H_3O (97), 11:1, 98; Ph (88), 8:1, 98; (*E*)-PhCH=CH (95), 10:1, 98	126

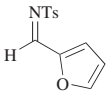
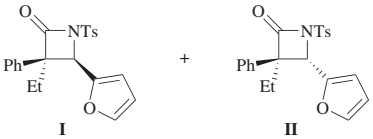
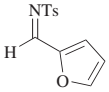
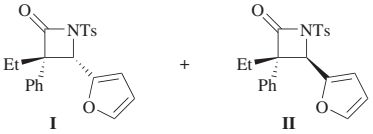
TABLE 8C. HETEROCYCLIC CARBENE-CATALYZED CYCLOADDITIONS TO IMINES

Ketene	Imine	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_9				
		**15** (10 mol %), Cs_2CO_3 (10 mol %), THF, rt	 **I** + **II** (53), **I/II** = 86:14, 93% ee **I**	129
C_{10}				
		15 (10 mol %), Cs_2CO_3 (10 mol %), THF, rt		129

R	I + II	I/II	% ee I
2-furyl	(57)	83:17	98
Ph	(64)	75:25	99
2-ClC_6H_4	(71)	91:9	99
4-ClC_6H_4	(72)	75:25	96
3-ClC_6H_4	(66)	80:20	99
2-BrC_6H_4	(58)	94:6	97
4-BrC_6H_4	(71)	78:22	99
4-$O_2NC_6H_4$	(75)	71:29	99

		**15** (10 mol %), Cs_2CO_3 (10 mol %), THF, rt		129

R	I + II	I/II	% ee I
2-ClC_6H_4	(61)	99:1	97
4-ClC_6H_4	(53)	83:17	99

		**42** (20 mol %), *t*-BuOK (20 mol %), THF, rt	 **I** + **II** (93), **I/II** = 55:45, 38% ee **I**	129
		**43** (20 mol %), base (20 mol %), THF		129

Base	I + II	I/II	% ee I
t-BuOK	(99)	62:38	42
Cs_2CO_3	(99)	78:22	63

TABLE 8C. HETEROCYCLIC CARBENE-CATALYZED CYCLOADDITIONS TO IMINES (*Continued*)

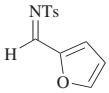
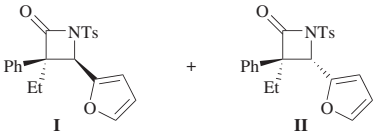
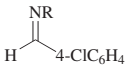
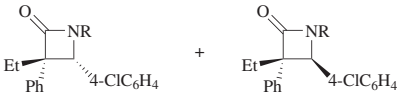
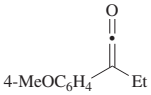
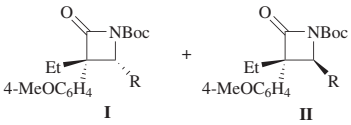
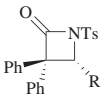
Ketene	Imine	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_{10}				
		**44** (20 mol %), Cs_2CO_3 (20 mol %), THF, rt	 **I** + **II** (59), **I/II** = 55:45, 9% ee **I**	129
		Cat. (20 mol %), Cs_2CO_3 (20 mol %), THF, rt	**I** + **II**	129
			Cat. R **I + II** **I/II** % ee **I** **15** 2-C_4H_3O (98) 67:33 83 **15a** 2-C_4H_3O (99) 50:50 58 **15** 4-ClC_6H_4 (97) 36:64 19	
		**15** (20 mol %), Cs_2CO_3 (20 mol %), THF	 **I** + **II**	129
			R **I + II** **I/II** % ee **I** Cbz (53) 60:40 89 Boc (68) 75:25 95	
		**15** (10 mol %), Cs_2CO_3 (10 mol %), THF, rt	 **I** + **II**	129
			R **I + II** **I/II** % ee **I** 2-ClC_6H_4 (78) 93:7 91 2,4-$Cl_2C_6H_3$ (62) 89:11 96	
C_{14}				
		Catalyst (10 mol %), KHMDS (9 mol %), Et_2O, rt	 R Catalyst % ee 2-C_4H_3O **45** (85) 61 2-C_4H_3O **46** (93) 55 Ph **45** (90) 58 Ph **46** (96) 64 4-BrC_6H_4 **45** (79) 56 4-BrC_6H_4 **46** (96) 57 2-Np **45** (95) 73 2-Np **46** (92) 75	130

TABLE 9. [4 + 2] CYCLOADDITIONS TO *O*-BENZOQUINONES AND *O*-BENZOQUINONE IMINE DIENES

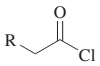
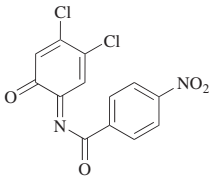
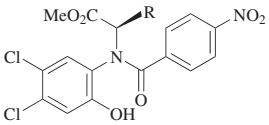
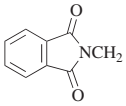
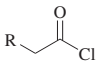
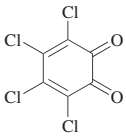
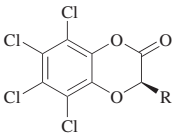
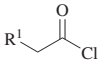
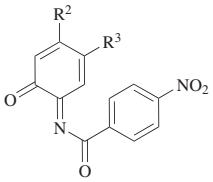
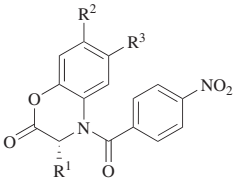
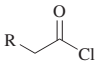
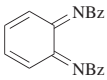
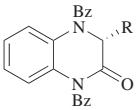
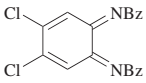
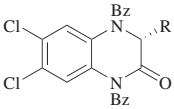
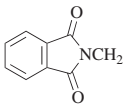
Ketene Source	Diene	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
*Please refer to the charts preceding the tables for structures indicated by the **bold** numbers.*				
C_{3-9}				
		1. **40** (10 mol %), $Sc(OTf)_3$ (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78° 2. MeOH	 >99% ee	137
			R: Me (91); Et (86); *i*-Pr (84); Ph (92); 4-$MeOC_6H_4$ (87); Bn (81);  (90)	
C_{4-9}				
		**40** (10 mol %), $i\text{-}Pr_2NEt$, THF, –78°		134
			R: Et (91) 99; *i*-Pr (75) 93; Ph (90) 90; 4-$MeOC_6H_4$ (58) 99; 4-MeC_6H_4 (75) 93; Bn (72) 99	
		**40** (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78°	 >99% ee	136
			R^1 R^2 R^3: Et H CF_3 (62); *i*-Bu Cl Cl (65); Bn H *t*-Bu (61)	
		**40** (10 mol %), $Zn(OTf)_2$ (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78°	 >99% ee	135
			R: Et (76); *i*-Pr (71); *i*-Bu (73); Bn (83)	
		**40** (10 mol %), $Zn(OTf)_2$ (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78°	 >99% ee	135
			R: $MeSCH_2$ (84); Et (82); *i*-Pr (79); $Cl(CH_2)_3$ (81); $PhCH_2$ (85);  (93)	

TABLE 9. [4 + 2] CYCLOADDITIONS TO *ORTHO*-BENZOQUINONE IMINES (*Continued*)

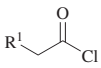
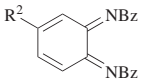
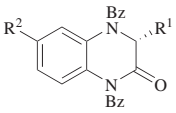
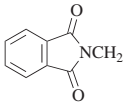
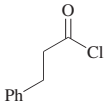
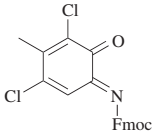
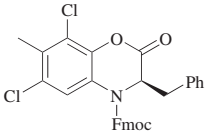
Ketene Source	Diene	Conditions	Product(s), Yield(s) (%), and Stereoselectivity				Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*							
C_{4-9}							
		**12** (10 mol %), $Zn(OTf)_2$ (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78°	 >99% ee	R^1	R^2		135
				Et	CF_3	(81)	
				Et	Bz	(84)	
				$MeSCH_2$	Cl	(62)	
				$MeSCH_2$	Bz	(92)	
				i-Pr	CF_3	(79)	
				i-Pr	Bz	(84)	
				$Cl(CH_2)_3$	Bz	(87)	
				i-Bu	CF_3	(83)	
				i-Bu	Bz	(84)	
				Bn	CF_3	(77)	
				Bn	Bz	(86)	
				$4\text{-}BrC_6H_4CH_2$	CF_3	(78)	
				$4\text{-}BrC_6H_4CH_2$	Bz	(69)	
					Bz	(90)	
C_9							
		**40** (10 mol %), $(i\text{-Pr})_2NEt$, THF, –78°		(63) >99% ee			136

TABLE 10. [4 + 2] CYCLOADDITIONS TO THIOACYL IMINES

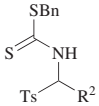
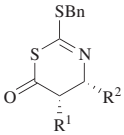
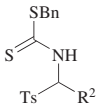
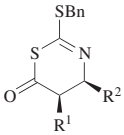
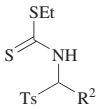
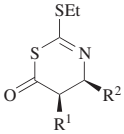
Ketene Source	Imine Precursor	Conditions	Product(s), Yield(s) (%), and Stereoselectivity					Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*								
C_{3-4}								
		**6** (20 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°		R^1	R^2	dr	% ee	139
				Me	*i*-Bu (74)	>97:3	95	
				Et	Ph (59)	>97:3	>98	
C_{3-5}								
		**5** (20 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 dr >97:3	R^1	R^2		% ee	139
				Me	*n*-Pr	(67)	98	
				Et	*i*-Bu	(72)	>98	
				n-Pr	$PhCH_2CH_2$	(58)	>98	
				i-Pr	$PhCH_2CH_2$	(63)	>98	
C_{3-9}								
		**5** (20 mol %), $LiClO_4$, $(i\text{-Pr})_2NEt$, CH_2Cl_2/Et_2O (9:1), –78°	 >98% ee	R^1	R^2		dr	139
				Me	$c\text{-}C_6H_{11}$	(75)	95:5	
				Me	$PhCH_2CH_2$	(76)	95:5	
				Me	$BnOCH_2$	(51)	>97:3	
				Me	Ph	(59)	>97:3	
				Et	$PhCH_2CH_2$	(68)	>97:3	
				Bn	$PhCH_2CH_2$	(65)	>97:3	

TABLE 11. [4 + 2] CYCLOADDITIONS OF VINYL KETENES

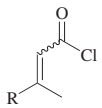
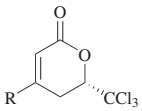
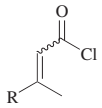
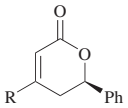
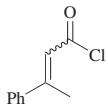
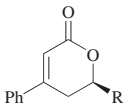
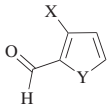
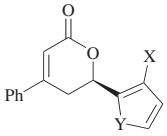
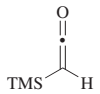
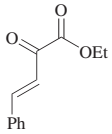
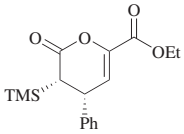
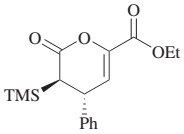
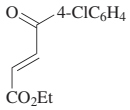
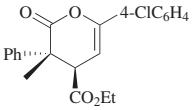
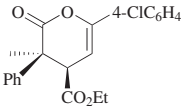
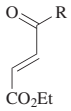
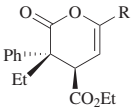
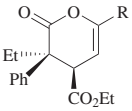
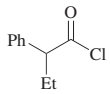
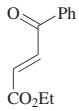
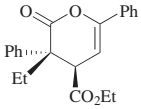
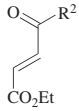
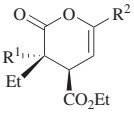
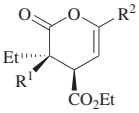
Ketene Source	Dienophile	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_{4-10}				
		**6** (*x* mol %), $Sn(OTf)_2$ (*y* mol %), $(i\text{-Pr})_2NEt$, toluene, –15°		143
			R / *x* / *y* / % ee: Et_3Si 40 20 (43) 96; Et_3Si 100 30 (54) 96; *n*-Pr_3Si 100 30 (51) 97; *n*-Bu_3Si 100 30 (61) 97; $BnMe_2Si$ 100 30 (47) 92; Et 20 10 (60) 54; *i*-Pr 20 10 (78) 82; *i*-Bu 40 20 (73) 70; *t*-Bu 20 10 (58) 95; *t*-Bu 40 20 (80) 95; *c*-C_6H_{11} 20 10 (75) 83; Ph 20 10 (73) 81	
C_{5-10}				
		**47** (20 mol %), $Er(OTf)_3$ (1.5 eq), $(i\text{-Pr})_2NEt$, THF/toluene (1:1), –10°		144
			R / % ee: Me (24) 95; Et (62) 95; *i*-Pr (56) 95; *i*-Bu (54) 98; *c*-C_6H_{11} (65) 96	
C_{10}				
		**47** (*x* mol %), $Er(OTf)_3$ (1.5 eq), $(i\text{-Pr})_2NEt$, THF/toluene (1:1), –10°		144
			R / *x* / % ee: Ph 10 (64) 94; 2-$O_2NC_6H_4$ 20 (91) 91; 4-$O_2NC_6H_4$ 20 (72) 88; 2-ClC_6H_4 10 (77) 88; 3-ClC_6H_4 20 (78) 93; 4-ClC_6H_4 10 (71) 92; 3-BrC_6H_4 20 (77) 95; 4-BrC_6H_4 10 (70) 93; 4-$MeOC_6H_4$ 20 (26) 94; 4-MeC_6H_4 20 (30) 94; 3-$CF_3C_6H_4$ 10 (87) 93; (*E*)-4-$O_2NC_6H_4CH{=}CH$ 20 (62) 92; 2-Np 20 (55) 95	
		**47** (*x* mol %), $Er(OTf)_3$ (1.5 eq), $(i\text{-Pr})_2NEt$, THF/toluene (1:1), –10°		144
			X / Y / *x* / % ee: H O 10 (23) 94; H S 20 (40) 95; Br S 20 (46) 96	

TABLE 12. [4 + 2] CYCLOADDITIONS TO ENONES

Ketene Source	Enone	Conditions	Product(s), Yield(s) (%), and Stereoselectivity	Refs.
Please refer to the charts preceding the tables for structures indicated by the ***bold*** *numbers.*				
C_2				
		**24** (20 mol %), $AgSbF_6$ (44 mol %), CH_2Cl_2, –78°	 **I** +  **II** **I** + **II** (96), **I/II** > 95:5, 97% ee **I**	104
C_9				
		**15** (10 mol %), Cs_2CO_3 (20 mol %), THF, 0° to rt	 **I** +  **II** **I** + **II** (82), **I/II** > 99:1, 84% ee	141
C_{10}				
		**15** (10 mol %), Cs_2CO_3 (20 mol %), THF, 0° to rt	 **I** +  **II** R | **I** + **II** | **I/II** | % ee **I** 2-C_4H_3O | (78) | 39:1 | 92 Ph | (79) | 24:1 | 91 4-ClC_6H_4 | (70) | 18:1 | 90 4-BrC_6H_4 | (68) | 22:1 | 87 4-$O_2NC_6H_4$ | (61) | 20:1 | 91 4-MeC_6H_4 | (69) | 25:1 | 90	141
		1. Et_3N (20 eq), THF, rt 2. **15** (20 mol %), Cs_2CO_3 (40 mol %), THF, rt	 (77) >20:1 dr, 88% ee	141
		**15** (10 mol %), Cs_2CO_3 (20 mol %), THF, 0° to rt	 **I** +  **II** R^1 | R^2 | **I** + **II** | **I/II** | % ee **I** 4-ClC_6H_4 | 4-ClC_6H_4 | (74) | 15:1 | 89 4-ClC_6H_4 | Ph | (93) | 17:1 | 91 4-$MeOC_6H_4$ | Ph | (57) | 16:1 | 91	141

REFERENCES

[1] Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.
[2] Woodward, R. B.; Hoffmann, R. *Conservation of Orbital Symmetry*; Verlag Chemie: Academic Press: New York, 1970.
[3] Tidwell, T. T. *Ketenes II*; John Wiley & Sons: Hoboken, 2006.
[4] Dehmlow, E. V.; Slopianka, M.; Pickardt, J. *Liebigs Ann. Chem.* **1979**, 572.
[5] Eckert, W. R.; Strauß, H. J. *Tetrahedron Lett.* **1971**, 12, 1265.
[6] Andreades, S.; Carlson, H. D. *Org. Synth.* **1973**, *Coll. Vol. 5*, 679.
[7] Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545.
[8] France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
[9] Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655.
[10] Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465.
[11] Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771.
[12] Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159.
[13] Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.
[14] Paull, D. H.; Wolfer, J.; Grebinski, J. W.; Weatherwax, A.; Lectka, T. *Chimia* **2007**, *61*, 240.
[15] Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272.
[16] Pons, J.-M.; Pommier, A.; Rajzmann, M.; Liotard, D. J. *J. Mol. Struct. (Theochem)* **1994**, *313*, 361.
[17] Lecea, B.; Arrieta, A.; Roa, G.; Ugalde, J. M.; Cossio, F. P. *J. Am. Chem. Soc.* **1994**, *116*, 9613.
[18] Lecea, B.; Arrieta, A.; Arrastia, I.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 5216.
[19] Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.
[20] Staudinger, H. *Chem. Ber.* **1907**, *40*, 1145.
[21] Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51.
[22] Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735.
[23] Gong, L.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, *113*, 6021.
[24] McAllister, M. A.; Tidwell, T. T. *J. Org. Chem.* **1994**, *59*, 4506.
[25] Firl, J.; Runge, W. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 668.
[26] Allred, E. L.; Grant, D. M.; Goodlett, W. *J. Am. Chem. Soc.* **1965**, *87*, 673.
[27] Lecea, B.; Arrieta, A.; Lopez, X.; Ugalde, J. M.; Cossio, F. P. *J. Am. Chem. Soc.* **1995**, *117*, 12314.
[28] Pons, J.-M.; Oblin, M.; Pommier, A.; Rajzmann, M.; Liotard, D. *J. Am. Chem. Soc.* **1997**, *119*, 3333.
[29] Singleton, D. A.; Wang, Y.; Yang, H. W.; Romo, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1572.
[30] Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2233.
[31] Qiao, G. G.; Andraos, J.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 5634.
[32] Viser, P.; Zuhse, R.; Wong, M. W.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 12598.
[33] Wagner, B. D.; Arnold, B. R.; Brown, G. S.; Lusztyk, J. *J. Am. Chem. Soc.* **1998**, *120*, 1827.
[34] Pracejus, H. *Fortschr. Chem. Forsch.* **1967**, *8*, 493.
[35] Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157.
[36] Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
[37] Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
[38] Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619.
[39] Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761.
[40] Liu, C. M.; Smith, III, W. J.; Gustin, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 5770.
[41] Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.
[42] Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199.
[43] Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
[44] Palomo, C.; Miranda, J. I.; Cuevas, C.; Odriozola, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1735.
[45] Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Volante, R. P.; Smith, G. B.; Shinkay, I.; Tschaen, D. M. *J. Org. Chem.* **1989**, *54*, 3792.
[46] Cossío, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925, and references therein.

[47] López, R.; Sordo, T. L.; Sordo, J. A.; González, J. *J. Org. Chem.* **1993**, *58*, 7036.
[48] Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 5869.
[49] Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988, and references therein.
[50] Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161.
[51] Martin-Zamora, E.; Ferrete, A.; Llera, J. M.; Munoz, J. M.; Pappalardo, R. R.; Fernandez, R.; Lassaletta, J. M. *Chem.—Eur. J.* **2004**, *10*, 6111.
[52] Fernandez, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martin-Zamora, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 831.
[53] *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley & Sons: New York, 1994.
[54] Danishefsky, S. J. *Chemtracts* **1989**, 273.
[55] Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.
[56] Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Prekel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779.
[57] Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810.
[58] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
[59] Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380.
[60] Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.
[61] Young, F. G. *J. Am. Chem. Soc.* **1949**, *71*, 1346.
[62] Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444.
[63] Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.
[64] Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977.
[65] Ketelaar, P. E. F.; Staring, E. G. J.; Wynberg, H. *Tetrahedron Lett.* **1985**, *26*, 4665.
[66] Taggi, A. E.; Hafez, A. M.; Wack, H; Young, B.; Ferraris, D; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626.
[67] Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.
[68] Armstrong, A.; Geldart, S. P.; Jenner, C. R.; Scutt, J. N. *J. Org. Chem.* **2007**, *72*, 8091.
[69] Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth.* **1988**, *Coll. Vol. 6*, 549.
[70] MacMillan, D. W. C. *Nature* **2008**, *455*, 304.
[71] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem.* Soc. **1957**, *79*, 1920.
[72] Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.
[73] Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809.
[74] Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.
[75] Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438.
[76] Masamune, S.; Choy, W.; Petersen, J. S.; Sita. L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.
[77] Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.
[78] Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.
[79] Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6358.
[80] Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029.
[81] Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945.
[82] Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731.
[83] Zhang, W.; Matla, A. S.; Romo, D. *Org. Lett.* **2007**, *9*, 2111.
[84] Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.
[85] Jenkins, A. D. *J. Chem. Soc.* **1952**, 2563.
[86] McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1600.
[87] Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5*, 4745.
[88] Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549.
[89] Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715.
[90] Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777.
[91] Elam, E. U. *J. Org. Chem.* **1967**, *32*, 215.
[92] Zaitseva, G. S.; Vinokurova, N. G.; Baukov, Y. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, *45*, 1372; *Zh. Obshch. Khim.* **1975**, *45*, 1398.
[93] Zaitseva, G. S.; Vasil'eva, L. I.; Vinokurova, N. G.; Safronova, O. A.; Baukov, Y. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1978**, *48*, 1249; *Zh. Obshch. Khim.* **1978**, *48*, 1363.

[94] Hannay, N. B.; Smyth, C. P. *J. Am. Chem. Soc.* **1946**, *68*, 1357.
[95] Walsh, A. D. *J. Am. Chem. Soc.* **1946**, *68*, 2408.
[96] Tamai, Y.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1549.
[97] Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2281.
[98] Pommier, A.; Kocienski, P. J.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2105.
[99] Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998**, 1655.
[100] Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1053.
[101] Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255.
[102] Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998**, *39*, 2877.
[103] Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
[104] Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125.
[105] Nelson, S. G.; Peelen, T. J.; Wan. Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742.
[106] Nelson, S. G.; Wan. Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535.
[107] Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, *40*, 6541.
[108] Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, 2, 1883.
[109] Nelson, S. G.; Kim, B.-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318.
[110] Hoffmann, H. M. R.; Tsushima, T. *J. Am. Chem. Soc.* **1977**, *99*, 6008.
[111] Dehmlow, E. V.; Fastabend, U. *Synth. Commun.* **1993**, *23*, 79.
[112] Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14.
[113] Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1.
[114] Kull, T.; Peters, R. *Adv. Synth. Catal.* **2007**, *349*, 1647.
[115] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
[116] Kull, T.; Peters, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 5461.
[117] France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.
[118] Taggi, A. E.; Hafez, A. M.; Wack, H; Young, B.; Drury III, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
[119] France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R; Lectka, T. *Org. Lett.* **2002**, *4*, 1603.
[120] France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.
[121] Wack, H; France, S.; Hafez, A. M.; Drury III, W. J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, *69*, 4531.
[122] Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627.
[123] Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387.
[124] Hafez, A. M.; Dudding, T.; Wagerle, T. R; Shah, M. H.; Taggi, A. E.; Lectka, T. *J. Org. Chem.* **2003**, *68*, 5819.
[125] Huang, Y.; Calter, M. A. *Tetrahedron Lett.* **2007**, *48*, 1657.
[126] Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.
[127] Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.
[128] Nelson, D. A. *J. Org. Chem.* **1972**, *37*, 1447.
[129] Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.
[130] Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108.
[131] West, K. F.; Moore, H. W. *J. Org. Chem.* **1984**, *49*, 2809.
[132] Reid, W.; Radt, W. *Liebigs Ann. Chem.* **1965**, *688*, 170.
[133] Friedrichsen, W.; Oeser, H.-G. *Chem. Ber.* **1975**, *108*, 31.
[134] Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 1810.
[135] Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 13370.
[136] Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 7398.

[137] Paull, D. H.; Alden-Danforth, E.; Wolfer, J.; Dogo-Isonagie, C.; Abraham, C. J.; Lectka, T. *J. Org. Chem.* **2007**, *72*, 5380.
[138] Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. *Heterocycles* **2000**, *53*, 2667.
[139] Xu, X.; Wang, K.; Nelson, S. G. *J. Am. Chem. Soc.* **2007**, *129*, 11690.
[140] Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.
[141] Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473.
[142] Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690.
[143] Tiseni, P. S.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 5325.
[144] Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019.
[145] Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620.
[146] Chandra, B.; Fu, D.; Nelson S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2591.
[147] Vargo, T. R.; Hale, J. S.; Nelson, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 8678.
[148] Calter, M. A.; Guo, X.; Liao, W. *Org. Lett.* **2001**, *3*, 1499.
[149] Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500.
[150] Calter, M. A.; Guo, X. *Tetrahedron* **2002**, *58*, 7093.
[151] Calter, M. A.; Song, W.; Zhou, J. *J. Org. Chem.* **2004**, *69*, 1270.
[152] Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127.
[153] Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, 124, 13654.
[154] Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441.
[155] Bodner, M. J.; Phelan, R. M.; Townsend, C. A. *Org. Lett.* **2009**, *11*, 3606.
[156] Berks, A. H. *Tetrahedron* **1996**, *52*, 331.
[157] *The Organic Chemistry of* β*-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993.
[158] *Synthesis of* β*-Lactam Antibiotics: Chemistry, Biocatalysis and Process Integration*; Bruggink, A., Ed.; Kluwer: Dordrecht, 2001.
[159] Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.
[160] Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787.
[161] Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307.
[162] Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.
[163] Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunoguès, J.; Picard, J.-P.; Ricci, A.; Seconi, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1239.
[164] Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem.—Eur. J.* **1997**, *3*, 1432.
[165] Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R. *Chem. Commun.* **1997**, 233.
[166] Capperucci, A.; Ricci, A.; Seconi, G.; Dunoguès, J.; Grelier, S.; Picard, J.-P.; Palomo, C.; Aizpurua, J.-M. *J. Organomet. Chem.* **1993**, *458*, C1.
[167] Dal Colle, M.; Distefano, G.; Jones, D.; Guerinno, A.; Seconi, G.; Modelli, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 789.
[168] Bongini, A.; Panunzio, M.; Piersanti, G.; Bandini, E.; Martelli, G.; Spunta, G.; Venturini, A. *Eur. J. Org. Chem.* **2000**, 2379.
[169] Bongini, A.; Panunzio, M.; Tamanini, E.; Martelli, G.; Vicennati, P. Monaru, M. *Tetrahedron: Asymm.* **2003**, *14*, 993.
[170] Palomo, C.; Ganboa, I.; Kot, A.; Dembkowski, L. *J. Org. Chem.* **1998**, *63*, 6398.
[171] Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161.
[172] del Pozo, C.; Macías, A.; López-Ortiz, F.; Maestro, M. Á.; Alonso, E.; González, J. *Eur. J. Org. Chem.* **2004**, 535.
[173] Hashimoto, Y.; Kai, A.; Saigo, K. *Tetrahedron Lett.* **1995**, *36*, 8821.
[174] Martín-Zamora, E.; Ferrete, A.; Llera, J. M.; Muñoz, J. M.; Pappalardo, R. R.; Fernández, R.; Lassaletta, J. M. *Chem.—Eur. J.* **2004**, *10*, 6111.
[175] Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 831.
[176] Fernández, R.; Ferrete, A.; Llera, J. M.; Magriz, A.; Martín-Zamora, E.; Díez, E.; Lassaletta, J. M. *Chem.—Eur. J.* **2004**, *10*, 737.
[177] Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2893.

[178] Díez, E.; Fernández, R.; Marqués-López, E.; Martín-Zamora, E.; Lassaletta, J. M. *Org. Lett.* **2004**, *6*, 2749.
[179] Reetz, M. T.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079.
[180] Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019.
[181] Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537.
[182] Kocienski, P. J.; Pelotier, B.; Pons, J.-M.; Prideaux, H. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1373.
[183] Pommier, A.; Pons, J.-M. *Synthesis*, **1994**, 1294.
[184] Palomo, C.; Miranda, J. I.; Cuevas, C.; Odriozola, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1735.
[185] Gilman, H.; Speeter, H. *J. Am. Chem. Soc.* **1943**, *65*, 2255.
[186] Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325.
[187] Jan, S.-Z.; Ma, C.; Wang, Y.-G. *Synthesis* **2005**, 725.
[188] Yuan, Q.; Jian, S.-Z.; Wang, Y.-G. *Synlett* **2006**, 1113.
[189] Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 4095.
[190] Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461.
[191] Gouge, V.; Jubault, P.; Quirion, J.-C. *Tetrahedron Lett.* **2004**, *45*, 773.
[192] Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773.
[193] Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030.
[194] Iza, A.; Vicario, J. L.; Carrillo, L.; Badia, D. *Synthesis* **2006**, 4065.
[195] Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339.
[196] Evans, D. A.; Kim, A. S. In *Handbook of Reagents for Organic Synthesis*; Coates, R. M., Denmark, S. E., Eds.; John Wiley & Sons: Chichester, 1999; pp 91–101.
[197] Zappia, G.; Cancelliere, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Synth.* **2007**, *4*, 238.
[198] Thiruvengadam, T. K.; McAllister, T.; Tan, C.-H. US Patent 5,728,827 (1998).
[199] Abrahams, I.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1994**, *50*, 12755.
[200] Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060.
[201] Tomioka, K.; Hussein, M. A.; Kambara, T.; Fujieda, H.; Hayashi, S.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715.
[202] Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.
[203] Cordóva, A. *Acc. Chem. Res.* **2004**, *37*, 102.
[204] Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.
[205] Notz, W.; Tanaka, F.; Watanabe, S.-i.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, *68*, 9624.
[206] Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2008**, *130*, 875.
[207] Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4.
[208] Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197.
[209] Nelson, S. G. *Tetrahedron: Asymm.* **1998**, *9*, 357.
[210] Kinugasa, M.; Hashimoto, S. *J. Chem. Soc, Chem. Commun.* **1972**, 466.
[211] Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382.
[212] Okuro, K.; Enna, M.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1107.
[213] Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2198.
[214] Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. *Synlett* **2007**, 2321.
[215] Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.
[216] Pfaltz, A. In *Asymmetric Synthesis–The Essentials*; Christmann, M., Bräse, S., Eds.; Wiley–VCH: Weinheim, 2007; pp 131–135.
[217] Ghosh, A. K.; Bilcer, G.; Fidanze, S. In *Chemistry of Heterocyclic Compounds*; Palmer, D. C., Ed.; John Wiley & Sons: New York, 2004; pp 529–594.
[218] Evans, D. A.; Kleinbeck, F.; Ruping, M. In *Asymmetric Synthesis–The Essentials*; Christmann, M., Bräse, S., Eds.; Wiley–VCH: Weinheim, 2008; pp 77–82.
[219] Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

[220] Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.
[221] Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 4082.
[222] Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071.
[223] Ye, M.-C.; Zhou, J.; Huang, Z.-Z.; Tang, Y. *Chem. Commun.* **2003**, 2554.
[224] Chiacchio, U.; Padwa, A.; Romeo, G. *Curr. Org. Chem.* **2009**, *13*, 422.
[225] Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147.
[226] Pellissier, H. *Tetrahedron* **2009**, *65*, 2839.
[227] Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807.
[228] Bazán-Tejeda, B.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem.—Eur. J.* **2006**, *12*, 8358.
[229] Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
[230] Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3124.
[231] Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288.
[232] Lin, L.; Fan, Q.; Qin, B.; Feng, X. *J. Org. Chem.* **2006**, *71*, 4141.
[233] Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185.
[234] Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X. *Eur. J. Org. Chem.* **2005**, 3542.
[235] Audrain, H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 11543.
[236] Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3059.
[237] Keck, G. E.; Yu, T. *Org. Lett.* **1999**, *1*, 289.
[238] Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *05*, 122.
[239] Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, 107, 5391.
[240] Staudinger, H. *Chem. Ber.* **1911**, *44*, 1619.
[241] Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122.
[242] Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.